COMMONWEALTH OF AUSTRALIA

P/00/001
Section 29

The Patents Act 1990

PATENT REQUEST: CONVENTION PATENT

We, DR KARL THOMAE GmbH, being the person identified below as the Applicant, request the grant of a patent to the person identified below as the Nominated Person, for an invention described in the accompanying standard complete specification
Full application details follow:-

Applicant:	DR KARL THOMAE GmbH
Address:	D-88397 Biberach an der Riss, Germany
Nominated Person:	DR KARL THOMAE GmbH
Address:	D-88397 Biberach an der Riss, Germany
Invention Title:	Carboxylic Acid Derivatives
Names of actual Inventors:	Frank Himmelsbach; Gunter Linz; Volkhard Austel; Helmut Pieper; Thomas Muller; Johannes Weisenberger; Brian Guth
Address for service in Australia:	CALLINAN LAWRIE, 278 High Street, Kew 3101, Victoria, Australia
Attorney Code:	CL

Convention Details

Basic Applicant	Application Number	Country	Country Code	Date of Application
DR KARL THOMAE GmbH	P 42 41 632.9	Germany	DE	10 December 1992

D A T E D this 8th day of December, 1993.

DR KARL THOMAE GmbH
By their Patent Attorneys:
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AUSTRALIA

PATENT

NOTICE OF ENTITLEMENT

We, DR. KARL THOMAE GmbH, of D-7950 Biberach an der Riss, Germany, being the applicant and the person nominated for grant of patent in respect of the Application for an invention entitled **CARBOXYLIC ACID DERIVATIVES**

state the following:-

STANDARD CONVENTION FILING

(a) The person nominated for the grant of the patent:

(i) has entitlement from the actual inventors by virtue of being a person who would, if a patent were to be granted upon an application made by the said inventors, be entitled to have the patent assigned to it; and

(ii) is the applicant of the basic application.

(b) The basic application listed on the request form is the first application made in a Convention country in respect of the invention.

Jeffrey A. Ryder 10 December 1993.

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Jeffrey A. Ryder
Registered Patent Attorney

Date

To: The Commissioner of Patents

AU9352306

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(19) AUSTRALIAN PATENT OFFICE

(54) Title
CARBOXYLIC ACID DERIVATIVES

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(57) Claim

1. Compounds of formula I

$$A - B - C - D - E - COOR_a \qquad (I)$$

(wherein:

R_a denotes a hydrogen atom or a C_{1-5}-alkyl, C_{3-5}-alkenyl, phenyl(C_{1-3}-alkyl), C_{5-7}-cycloalkyl or R_1-CO-O-(R_2CH)- group;

R_1 denotes a C_{1-5}-alkyl, C_{5-7}-cycloalkyl, phenyl(C_{1-3}-alkyl), C_{1-5}-alkoxy, C_{5-7}-cycloalkoxy or phenyl group;

R_2 denotes a hydrogen atom or a C_{1-4}-alkyl, C_{5-7}-cycloalkyl or phenyl group;

A denotes a C_{1-5}-aminoalkyl group linked to group B via a carbon atom of A, or A denotes a 5-, 6- or 7-membered azacycloalkyl group linked to group B via a carbon atom of the azacycloalkyl group, or A denotes a quinuclidinyl or pyridyl group, wherein the nitrogen in the above-

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mentioned aminoalkyl or azacycloalkyl groups is optionally substituted by a group R_b, wherein the carbon atoms of the azacycloalkyl group are optionally substituted by 1 to 3 C_{1-3}-alkyl groups or by an aminocarbonyl, cyano, R_3O- or R_3O-CO- group,

wherein, in a 6- or 7-membered azacycloalkyl group A a >CH- unit in the 4-position relative to the ring nitrogen is optionally replaced by a nitrogen atom, wherein in a 5-, 6- or 7-membered azacycloalkyl group A a $-CH_2-CH<$ unit may be replaced by a -CH=C< unit and wherein in a piperazinyl or homopiperazinyl group A a ring carbon adjacent to the nitrogen atom in the 4-position is optionally oxo-substituted;
R_b denotes a C_{1-3}-alkyl, phenyl(C_{1-3}-alkyl), C_{2-4}-alkanoyl, trifluoroacetyl, (C_{1-5}-alkoxy)carbonyl, phenyl(C_{1-3}-alkoxy)carbonyl, (C_{3-5}-alkenyl)oxycarbonyl or an R_1-CO-O-(R_2CH)-O-CO- group;

R_3 denotes a hydrogen atom, or a C_{1-3}-alkyl or phenyl-(C_{1-3})-alkyl group,

B denotes a phenylene group optionally mono- or disubstituted by fluorine, chlorine or bromine atoms, by trifluoromethyl groups, or by C_{1-3}-alkyl, C_{1-3}-alkoxy, C_{1-3}-alkylsulphenyl, C_{1-3}-alkylsulphinyl or C_{1-3}-alkylsulphonyl groups, wherein the substituents may be identical or different and wherein, additionally, 1 or 2 unsubstituted methine groups may each be replaced by an N-atom, or B denotes a piperidinylene group,

C denotes a carbonyl, $-CH_2CH_2-$, -CH=CH-, $-CH_2-$, $-CH_2O-$, $-OCH_2-$, $-CONR_4-$, $-CONR_4-CH_2-$, $-NR_4CO-$, $-NR_4CO-NR_4-$, $-CH_2NR_4-$, $-NR_4CH_2-$, $-SO_2NR_4-$, $-SO_2NR_4-CH_2-$ or $-NR_4SO_2-$ group;

R_4 denotes a hydrogen atom or a C_{1-3}-alkyl or phenyl(C_{1-3}-alkyl) group, or if C denotes a $-CONR_4-$ group bound to group B via the carbonyl group, R_4 may also denote a methylene or 1,2-ethylene group bound to the carbon atom of group B in the ortho-position relative to the point

.../3

of linkage of the $-CONR_4-$ group;

D denotes a phenylene group optionally mono- or disubstituted by fluorine, chlorine or bromine atoms, by trifluoromethyl groups, by C_{1-3}-alkyl, C_{1-3}-alkoxy, C_{1-3}-alkylsulphenyl, C_{1-3}-alkylsulphinyl or C_{1-3}-alkylsulphonyl groups, wherein the substituents may be identical or different, and wherein additionally 1 or 2 unsubstituted methine groups may each be replaced by an N-atom, or D denotes a C_{5-7}-cycloalkylene group wherein one or two >CH- units may be replaced by an N-atom and additionally in an aza- or diazacyclohexylene ring thus formed, a ring carbon adjacent to a ring nitrogen is optionally oxo-substituted;

E denotes a bond, a C_{1-3}-alkyleneoxy group bound to group D through the oxygen atom, a straight-chain C_{1-5}-alkylene group optionally substituted by 1 or 2 C_{1-8}-alkyl groups, or by a hydroxy, C_{1-8}-alkoxy, R_5NH-, $R_5N(C_{1-8}alkyl)$ or $R_5N(phenylC_{1-3}-alkyl)$ group, or E denotes a C_{2-5}-alkenylene group optionally substituted by one or two C_{1-8}-alkyl groups;

R_5 denotes a hydrogen atom or a C_{1-8}-alkyl, (C_{1-4}-alkoxy)carbonyl, or phenyl(C_{1-3}-alkoxy)carbonyl group or a carbonyl or sulphonyl group substituted by a C_{1-8}-alkyl group or by a C_{3-7}-cycloalkyl, phenylC_{1-3}-alkyl or phenyl group, wherein each phenyl moiety in R_5 is optionally mono- or disubstituted by fluorine, chlorine or bromine atoms, by trifluoromethyl groups, or by C_{1-3}-alkyl, C_{1-3}-alkoxy, C_{1-3}-alkylsulphenyl, C_{1-3}-alkylsulphinyl or C_{1-3}-alkylsulphonyl groups and the substituents may be identical or different;

wherein

(i) if the A-B- moiety denotes a phenyl group substituted in the 4-position by an $R_b-NH-CH_2-$ group wherein R_b is a benzyloxycarbonyl group, then $R_8OOC-E-D-C-$ does not denote a 3-carboxy-phenylaminocarbonyl group,

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(ii) if the A-B- moiety denotes a phenyl group substituted in the 4-position by an R_b-NH-CH_2- group wherein R_b denotes a hydrogen atom or an acetyl group, then R_aOOC-E-D-C- does not represent a phenylcarbonyl group substituted in the 4-position by a carboxymethyl, methoxycarbonylmethyl, 2-carboxy-ethyl, 2-methoxycarbonyl-ethyl or 2-ethoxycarbonylethyl group,

(iii) if the A-B- moiety denotes a phenyl group substituted in the 4-position by an NH_2-CH_2-CH_2- group, then R_aOOC-E-D-C- does not denote a 4-ethoxycarbonyl-phenylcarbonyl group,

(iv) if the A-B- moiety denotes a 4-aminomethyl-phenyl-, 3-aminomethyl-phenyl-, 4-aminomethyl-3-methoxy-phenyl- or 3-aminomethyl-4-methoxyphenyl group, then R_aOOC-E-D-C- does not denote a 4-ethoxycarbonylmethoxy-2,3-dichlorophenylcarbonyl group,

(v) if the A-B- moiety denotes a phenyl group substituted in the 4-position by an NH_2-CH_2- or $(CH_3)_3$CO-CO-NH-CH_2- group, then R_aOOC-E-D-C- does not denote a 4-carboxyphenylmethoxy group,

(vi) if the A-B- moiety denotes a phenyl group substituted in the 4-position by an NH_2-CH_2- group, then R_aOOC-E-D-C- does not denote a 4-carboxy-phenylaminosulphonyl group,

(vii) if the A-B- moiety denotes a 4-(2-pyridyl)-phenyl- or 4-(3-pyridyl)-phenyl group, then R_aOOC-E-D-C- does not denote a 4-carboxy-phenylcarbonylamino, 4-benzyloxycarbonyl-phenylcarbonylamino- or 2-(4-carboxy-phenyl)-ethyl group, and

(viii) if the A-B- moiety denotes a 3-(4-pyridyl)-phenyl group, then R_aOOC-E-D-C- does not denote a 2-(carboxymethyl)-phenylcarbonylamino group)

and the isomers and salts thereof.

P/00/011
Regulation 3.2

AUSTRALIA

PATENTS ACT 1990

COMPLETE SPECIFICATION

FOR A STANDARD PATENT

ORIGINAL

TO BE COMPLETED BY APPLICANT

Name of Applicant: DR KARL THOMAE GmbH

Actual Inventor(s): Frank Himmelsbach; Gunter Linz; Volkhard Austel; Helmut Pieper; Thomas Muller; Johannes Weisenberger; Brian Guth

Address for Service: CALLINAN LAWRIE, 278 High Street, Kew, 3101, Victoria, Australia

Invention Title: "CARBOXYLIC ACID DERIVATIVES"

The following statement is a full description of this invention, including the best method of performing it known to me:-

60603.570

Carboxylic acid derivatives

This invention relates to novel carboxylic acid derivatives, their preparation, pharmaceutical compositions containing them and their use.

In EP-A-478328 and EP-A-478363 various phenylalanyl derivatives are described as fibrinogen antagonists.

It has now been found that certain novel carboxylic acid derivatives have valuable pharmacological properties, particularly aggregation-inhibiting effects. These new compounds differ structurally from the compounds described in EP-A-478328 and EP-A-478363, in particular in the group B in formula I below.

Thus viewed from one aspect the present invention provides compounds of formula I

$$A - B - C - D - E - COOR_a \qquad (I)$$

(wherein

R_a denotes a hydrogen atom or a C_{1-5}-alkyl, a C_{3-5}-alkenyl, phenyl(C_{1-3}-alkyl), C_{5-7}-cycloalkyl or a R_1-CO-O-(R_2CH)- group;

R_1 denotes a C_{1-5}-alkyl, C_{5-7}-cycloalkyl, phenyl(C_{1-3}-alkyl), C_{1-5}-alkoxy, C_{5-7}-cycloalkoxy or phenyl group;

R_2 denotes a hydrogen atom or a C_{1-4}-alkyl, C_{5-7}-cycloalkyl or phenyl group;

A denotes a C_{1-5}-aminoalkyl group linked to group B via a carbon atom of A, or A denotes a 5-, 6- or 7-membered azacycloalkyl group linked to group B via a carbon atom of the azacycloalkyl group, or A denotes a quinuclidinyl

or pyridyl group wherein, the nitrogen in the above-mentioned aminoalkyl or azacycloalkyl groups is optionally substituted by a group R_b, wherein the carbon atoms of the azacycloalkyl group are optionally substituted by 1 to 3 C_{1-3}-alkyl groups or by an aminocarbonyl, cyano, R_3O- or R_3O-CO- group,

wherein in a 6- or 7-membered azacycloalkyl group A a >CH- unit in the 4-position relative to the ring nitrogen is optionally replaced by a nitrogen atom, wherein in a 5-, 6- or 7-membered azacycloalkyl group A a $-CH_2-CH<$ unit is optionally replaced by a -CH=C< unit and wherein in a piperazinyl or homopiperazinyl group A a ring carbon adjacent to the nitrogen atom in the 4-position is optionally oxo-substituted;

R_b denotes a C_{1-3}-alkyl, phenyl(C_{1-3}-alkyl), C_{2-4}-alkanoyl, trifluoroacetyl, (C_{1-5}-alkoxy)carbonyl, phenyl(C_{1-3}-alkoxy)carbonyl, (C_{3-5}-alkenyl)oxycarbonyl, or R_1-CO-O-(R_2CH)-O-CO- group;

R_3 denotes a hydrogen atom or a C_{1-3}-alkyl or phenyl(C_{1-3}-alkyl) group;

B denotes a phenylene group optionally mono- or disubstituted by fluorine, chlorine or bromine atoms, by trifluoromethyl groups, or by C_{1-3}-alkyl, C_{1-3}-alkoxy, C_{1-3}-alkylsulphenyl, C_{1-3}-alkylsulphinyl or C_{1-3}-alkylsulphonyl groups, wherein the substituents may be identical or different and wherein, additionally, 1 or 2 unsubstituted methine groups may each be replaced by an N-atom, or B denotes a piperidinylene group,

C denotes a carbonyl, $-CH_2CH_2-$, -CH=CH-, $-CH_2-$, $-CH_2O-$, $-OCH_2-$, $-CONR_4-$, $-CONR_4-CH_2-$, $-NR_4CO-$, $-NR_4CO-NR_4-$, $-CH_2NR_4-$, $-NR_4CH_2-$, $-SO_2NR_4-$, $-SO_2NR_4-CH_2-$ or $-NR_4SO_2-$ group;

R_4 denotes a hydrogen atom or a C_{1-3}-alkyl or phenyl(C_{1-3}-alkyl) group, or if C denotes a $-CONR_4-$ group bound to group B via the carbonyl group, R_4 may also denote a methylene or 1,2-ethylene group bound to the carbon atom of group B in the ortho-position relative to the point of linkage of the $-CONR_4-$ group;

D denotes a phenylene group optionally mono- or disubstituted by fluorine, chlorine or bromine atoms, by trifluoromethyl groups, by C_{1-3}-alkyl, C_{1-3}-alkoxy, C_{1-3}-alkylsulphenyl, C_{1-3}-alkylsulphinyl or C_{1-3}-alkylsulphonyl groups, wherein the substituents may be identical or different, and wherein additionally 1 or 2 unsubstituted methine groups may each be replaced by an N-atom, or D denotes a C_{5-7}-cycloalkylene group wherein one or two >CH- units may be replaced by an N-atom and additionally in an aza- or diazacyclohexylene ring thus formed, a ring carbon adjacent to a ring nitrogen is optionally oxo-substituted;

E denotes a bond, a C_{1-3}-alkyleneoxy group bound to group D through the oxygen atom, a straight-chain C_{1-5}-alkylene group optionally substituted by 1 or 2 C_{1-8}-alkyl groups, or by a hydroxy, C_{1-8}-alkoxy, R_5NH-, $R_5N(C_{1-8}$alkyl) or R_5N(phenylC_{1-3}-alkyl) group, or E denotes a C_{2-5}-alkenylene group optionally substituted by one or two C_{1-8}-alkyl groups;

R_5 denotes a hydrogen atom or a C_{1-8}-alkyl, (C_{1-4}-alkoxy)carbonyl, or phenyl(C_{1-3}-alkoxy)carbonyl group or a carbonyl or sulphonyl group substituted by a C_{1-8}-alkyl group or by a C_{3-7}-cycloalkyl, phenylC_{1-3}-alkyl or phenyl group, wherein each phenyl moiety in R_5 is optionally mono- or disubstituted by fluorine, chlorine or bromine atoms, by trifluoromethyl groups, or by C_{1-3}-alkyl, C_{1-3}-alkoxy, C_{1-3}-alkylsulphenyl, C_{1-3}-alkylsulphinyl or C_{1-3}-alkylsulphonyl groups and the substituents may be

identical or different;

wherein

(i) if the A-B- moiety denotes a phenyl group substituted in the 4-position by an R_b-NH-CH_2- group, wherein R_b is a benzyloxycarbonyl group, then R_aOOC-E-D-C- does not denote a 3-carboxy-phenylaminocarbonyl group (see EP-A-0372486 and J. Med. Chem. 35: 4393-4407 (1992)), and

(ii) if the A-B- moiety denotes a phenyl group substituted in the 4-position by an R_b-NH-CH_2- group, wherein R_b denotes a hydrogen atom or an acetyl group, the R_aOOC-E-D-C- does not denote a phenylcarbonyl group substituted in the 4-position by a carboxymethyl, methoxycarbonylmethyl, 2-carboxy-ethyl, 2-methoxycarbonyl-ethyl or 2-ethoxycarbonylethyl group (see EP-A-0044541, JP-A-5813553, JP-A-5939866, JP-A-5846051 and Chem. Pharm. Bull. 33: 5059-5061 (1985)), and

(iii) if the A-B- moiety denotes a phenyl group substituted in the 4-position by an NH_2-CH_2-CH_2- group, then R_aOOC-E-D-C- does not denote a 4-ethoxycarbonyl-phenylcarbonyl group (see DE-A-3718638), and

(iv) if the A-B- moiety denotes a 4-aminomethyl-phenyl-, 3-aminomethyl-phenyl-, 4-aminomethyl-3-methoxy-phenyl- or 3-aminomethyl-4-methoxyphenyl group, then R_aOOC-E-D-C- does not denote a 4-ethoxycarbonylmethoxy-2,3-dichlorophenylcarbonyl group (see J. Med. Chem. 27: 1579-1587 (1984) and Diuretics: Chem. Pharmacol., Clin. Appl., Proc. Int. Conf. Diuretics, 1st, 21-29 (1984)), and

(v) if the A-B- moiety denotes a phenyl group substituted in the 4-position by an NH_2-CH_2- or $(CH_3)_3CO-CO-NH-CH_2-$ group, then $R_aOOC-E-D-C-$ does not denote a 4-carboxyphenylmethoxy group (see Int. J. Pept. Protein Res. 18: 451-458 (1981)), and

(vi) if the A-B- moiety denotes a phenyl group substituted in the 4-position by an NH_2-CH_2- group, then $R_aOOC-E-D-C-$ does not denote a 4-carboxy-phenylaminosulphonyl group (see Chem. Pharm. Bull (Tokyo) 7: 734-739 (1959) and J. Chem. Phys. 32: 691-697 (1960)), and

(vii) if the A-B- moiety denotes a 4-(2-pyridyl)-phenyl- or 4-(3-pyridyl)-phenyl group, then $R_aOOC-E-D-C-$ does not denote a 4-carboxy-phenylcarbonylamino, 4-benzyloxycarbonyl-phenylcarbonylamino- or 2-(4-carboxy-phenyl)-ethyl group (see J. Med. Chem. 11: 295 (1968) and US-A-2837522), and

(viii) if the A-B- moiety denotes a 3-(4-pyridyl)-phenyl group, then $R_aOOC-E-D-C-$ does not denote a 2-(carboxymethyl)-phenylcarbonylamino group (see Farmaco 44: 721-729 (1989)))

and the isomers (eg. tautomers and stereoisomers), isomer mixtures and salts thereof.

In formula I, where group D denotes an aza- or diazacyclohexylene ring this may be linked to groups C and E via ring carbons and/or ring nitrogens of D.

Preferred compounds according to the invention include those of formula I wherein:

R_a denotes a hydrogen atom or a C_{1-5}-alkyl, phenyl(C_{1-3}-alkyl) or C_{5-7}-cycloalkyl group;

A denotes a C_{2-5}-aminoalkyl group linked to group B via a carbon atom of A, or a piperidinyl group linked to group B via a carbon atom of the piperidinyl group, or A denotes a quinuclidinyl or pyridyl group, wherein the nitrogen of the above-mentioned aminoalkyl or piperidinyl groups is optionally substituted by a group R_b, wherein the carbon atoms of the piperidinyl group are optionally substituted by methyl, cyano, carboxy, methoxycarbonyl or aminocarbonyl groups,

and wherein in a piperidinyl A group a >CH- unit in the 4-position may be replaced by a nitrogen atom or a $-CH_2-CH<$ unit may be replaced by a $-CH=C<$ unit;

R_b denotes a C_{1-3}-alkyl, benzyl, (C_{1-5}-alkoxy)carbonyl, benzyloxycarbonyl or $CH_3-CO-O-(CH_2)-O-CO-$ group;

B denotes a phenylene group optionally substituted by a fluorine, chlorine or bromine atom or by a C_{1-2}-alkyl, C_{1-2}-alkoxy, C_{1-2}-alkylsulphenyl, C_{1-2}-alkylsulphinyl or C_{1-2}-alkylsulphonyl group, or B denotes a pyridinylene or piperidinylene group;

C denotes a $-CO-$, $-CH_2CH_2-$, $-CH=CH-$, $-CH_2-$, $-CH_2O-$, $-OCH_2-$, $-CONR_4-$, $-NR_4CO-$, $-NR_4CO-NR_4-$, $-CH_2NR_4-$, $-NR_4CH_2-$, $-SO_2NR_4-$ or $-NR_4SO_2-$ group;

R_4 denotes a hydrogen atom or a C_{1-2}-alkyl or phenyl(C_{1-2}-alkyl) group or, if C denotes a $-CONR_4$ group bound to group B via the carbonyl group, R_4 may also denote a methylene or 1,2-ethylene group bound to the carbon atom of group B in the ortho- position relative to the point of linkage of the $-CONR_4$ group;

D denotes a phenylene group optionally substituted by a chlorine or bromine atom, or by a C_{1-2}-alkyl or C_{1-2}-alkoxy group, or D denotes a cyclohexylene group in which one

or two >CH- units may be replaced by N-atoms, and additionally, in a piperidinylene or piperazinylene D group a ring carbon adjacent to a ring nitrogen is optionally oxo-substituted;

E denotes a bond, a methyleneoxy group bound to group D through the oxygen atom, a 1,2-ethenylene group or a straight-chain C_{1-5}-alkylene group which may be substituted by a C_{1-7}-alkyl group or by an R_5NH- group; and

R_5 denotes a hydrogen atom or a C_{1-7}-alkylcarbonyl, benzylcarbonyl, C_{1-5}-alkylsulphonyl or benzylsulphonyl group;

wherein

(iii) if the A-B- moiety denotes a phenyl group substituted in the 4-position by an $NH_2-CH_2-CH_2-$ group, then $R_aOOC-E-D-C$ does not denote a 4-ethoxycarbonyl-phenylcarbonyl group, and

(vii) if the A-B- moiety denotes a 4-(2-pyridyl)-phenyl- or 4-(3-pyridyl)-phenyl group, then $R_aOOC-E-D-C-$ does not denote a 4-carboxy-phenylcarbonylamino, 4-benzyloxycarbonyl-phenylcarbonylamino- or 2-(4-carboxy-phenyl)-ethyl group, and

(viii) if the A-B- moiety represents a 3-(4-pyridyl)-phenyl group, then $R_aOOC-E-D-C-$ does not denote a 2-(carboxymethyl)-phenylcarbonylamino group;

and the tautomers, stereoisomers (including mixtures thereof) and salts thereof.

In formula I, where group D denotes a piperidinylene or piperazinylene ring this may be linked to groups C and E via ring carbons and/or ring nitrogens of D.

Particularly preferred compounds according to the invention include those of formula I wherein:

R_a denotes a hydrogen atom or a C_{1-4}-alkyl, 2-phenylethyl or cyclohexyl group;

A denotes a C_{3-5}-aminoalkyl group linked to group B via a carbon atom of A, or a piperidinyl group linked to group B via a carbon atom of the piperidinyl group or A denotes a quinuclidinyl or 4-pyridyl group, wherein the nitrogen atom in the above-mentioned piperidinyl group is optionally substituted by a group R_b, wherein the carbon atoms of the piperidinyl group are optionally substituted by methyl, cyano, carboxy, methoxycarbonyl or aminocarbonyl groups,

and wherein in a piperidinyl A group a >CH- unit in the 4-position may be replaced by a nitrogen atom or a $-CH_2-CH<$ unit may be replaced by a $-CH=C<$ unit;

R_b denotes a C_{1-3}-alkyl, benzyl, (C_{1-4}-alkoxy)carbonyl or $CH_3-CO-O-(CH_2)-O-CO-$ group;

B denotes an optionally methyl- or methoxy- substituted phenylene group or a 2,5-pyridinylene or 1,4-piperidinylene group;

C denotes a $-CO-$, $-CH_2CH_2-$, $-CH=CH-$, $-CH_2-$, $-CH_2O-$, $-OCH_2-$, $-CONR_4-$, $-NR_4CO-$, $-NR_4CO-NR_4-$ or $-CH_2NR_4-$ group or an $-SO_2NR_4-$ group wherein the SO_2 moiety is linked to group B;

R_4 denotes a hydrogen atom or a methyl or 2-phenylethyl group or, if C denotes a $-CONR_4-$ group bound to group B via the carbonyl group, R_4 may also denote a methylene or 1,2-ethylene group bound to the carbon atom of group B in the ortho-position relative to the linkage point of the $-CONR_4-$ group;

D denotes a phenylene group or a cyclohexylene group in which one or two >CH- units may be replaced by N- atoms;

E denotes a bond, a methyleneoxy group bound to group D through the oxygen atom, or a straight-chain C_{1-5}-alkylene group which may be substituted by an R_5NH- group;

R_5 denotes a hydrogen atom or a (C_{1-5}-alkyl)carbonyl, C_{1-4}alkyl-sulphonyl, or benzylsulphonyl group;

and the tautomers, stereoisomers (including the mixtures thereof) and salts thereof.

In formula I, where group D denotes a piperidinylene or piperazinylene ring this may be linked to groups C and E via ring carbons and/or ring nitrogens of D.

Especially preferred compounds according to the invention include those of formula I wherein

R_a denotes a hydrogen atom or a C_{1-4}-alkyl or cyclohexyl group;

A denotes a piperidinyl or 3,4-dehydro-piperidinyl group linked to group B via the 4-position, wherein the nitrogen atom is optionally substituted by a group R_b or A denotes a 4-piperazinyl group optionally substituted by a group R_b in the 1-position, or A denotes a quinuclidinyl group;

R_b denotes a (C_{1-4}-alkoxy)carbonyl group;

B denotes a phenylene group;

C denotes a $-CONR_4$ group;

R_4 denotes a hydrogen atom or a methyl group or, if C denotes a $-CONR_4$ group bound to group B via the carbonyl group, R_4 may also represent a methylene or 1,2-ethylene group bound to the carbon atom of group B in the ortho-position relative to the point of linkage of the $-CONR_4$ group;

D denotes a 1,4-phenylene or 1,4-cyclohexylene group;

E denotes a bond or a 1,2-ethylene group optionally substituted by an R_5NH- group; and

R_5 denotes a (C_{1-5}-alkyl)carbonyl or a C_{1-4}-alkylsulphonyl group;

and the tautomers, stereoisomers (including mixtures thereof) and salts thereof.

More especially preferred compounds according to the invention include:

4-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine,

4-[4-[[4-[2-(n-butanesulphonylamino)-2-(methoxycarbonyl)-ethyl]-phenyl]-aminocarbonyl]-phenyl]-piperidine,

4-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine,

4-[4-[[4-[2-(n-butanesulphonylamino)-2-carboxyethyl]-phenyl]-aminocarbonyl]-phenyl]-piperidine,

4-[3-[[4-[2-(n-butanesulphonylamino)-2-carboxyethyl]-phenyl]-aminocarbonyl]-phenyl]-piperidine and

4-[3-[[4-[2-(n-butanesulphonylamino)-2-(methoxycarbonyl)-ethyl]-phenyl]-aminocarbonyl]-phenyl]-piperidine,

and the tautomers, stereoisomers (including mixtures thereof) and salts thereof.

Viewed from another aspect, the invention also provides a process for preparing the compounds of the invention, said process comprising at least one of the following steps:

a) (to prepare compounds of formula I wherein R_a denotes a hydrogen atom)

hydrolysing, pyrrolysing or hydrogenolysing a compound of formula II

$$A - B - C - D - E - COOR_a' \qquad (II)$$

(wherein
A, B, C, D and E are as hereinbefore defined and R_a' has the meanings given for R_a hereinbefore, with the exception of the hydrogen atom);

b) (to prepare compounds of formula I, wherein A is substituted by a group R_b)

reacting a compound of formula III

$$A_1 - B - C - D - E - COOR_a \qquad (III)$$

(wherein
B, C, D, E and R_a are as hereinbefore defined and

A_1 denotes a C_{1-5}-aminoalkyl group linked to group B via a carbon atom or a 5-, 6- or 7-membered azacycloalkyl group linked to group B via a carbon atom, wherein the carbon atoms of the azacycloalkyl group may be substituted by 1 to 3 C_{1-3}-alkyl groups or by an aminocarbonyl, cyano, R_3O- or R_3O-CO- group, wherein R_3 is as hereinbefore defined) with a compound of formula IV

$$R_b - Z_1 \qquad (IV)$$

(wherein
R_b is as hereinbefore defined and
Z_1 denotes a nucleophilic leaving group such as a halogen atom, e.g. a chlorine, bromine or iodine atom, or, if Z_1 is bound to a carbonyl group, Z_1 may also denote a hydroxy, alkanoyloxy or alkyloxycarbonyloxy group, or in the presence of a reducing agent when Z_1 together with an adjacent hydrogen atom of the group R_b denotes an oxygen atom);

c) (to prepare compounds of formula I, wherein R_a has the meanings given hereinbefore, with the exception of the hydrogen atom)

reacting a compound of formula V

$$A - B - C - D - E - COOH \qquad (V)$$

(wherein
A, B, C, D and E are as hereinbefore defined) with a

compound of formula VI

$$Z_2 - R_a' \qquad (VI)$$

(wherein
R_a' has the meanings given for R_a hereinbefore, with the exception of the hydrogen atom, and
Z_2 denotes a nucleophilic leaving group such as a halogen atom, e.g. a chlorine or bromine atom, or a sulphonyloxy group substituted at the sulphonyl group, e.g. a methanesulphonyloxy, methoxysulphonyloxy or toluenesulphonyloxy group, or a hydroxy group);

d) (to prepare compounds of formula I, wherein C denotes a $-CH_2-NH-$ group)

reducing a compound of formula VII

$$A - B - CH=N - D - E - COOR_a \qquad (VII)$$

(wherein
A, B, D, E and R_a are as hereinbefore defined);

e) (to prepare compounds of formula I, wherein C denotes a $-CO-NR_4-$ group)

reacting a compound of formula VIII

$$A_2 - B - COOH \qquad (VIII)$$

(wherein
B is as hereinbefore defined and

A_2 denotes a group A substituted at the nitrogen atom by an alkyl, aralkyl, alkanoyl, trifluoroacetyl or alkoxycarbonyl group) with an amine of formula IX

$$R_4 - NH - D - E - COOR_a' \qquad (IX)$$

(wherein
D, E and R_4 are as hereinbefore defined and
R_a' has the meanings given for R_a hereinbefore, with the exception of the hydrogen atom);

f) (to prepare compounds of formula I, wherein C denotes an $-NR_4-CO-$ group)

reacting a compound of formula X

$$A_2 - B - NH-R_4 \qquad (X)$$

(wherein
R_4 and B are as hereinbefore defined and
A_2 denotes a group A substituted at the nitrogen atom by an alkyl, aralkyl, alkanoyl, trifluoroacetyl or alkoxycarbonyl group) with a carboxylic acid of formula

$$HOOC - D - E - COOR_a' \qquad (XI)$$

(wherein
D and E are as hereinbefore defined and
R_a' has the meanings given for R_a hereinbefore with the exception of the hydrogen atom);

g) (to prepare compounds of formula I, wherein A denotes a C_{1-5}-aminoalkyl group linked to group B via a carbon atom)

reducing a compound of formula XII

$$A_3 - B - C - D - E - COOR_a \qquad (XII)$$

(wherein
B, C, D, E and R_a are as hereinbefore defined and

A_3 denotes a cyano group or cyanoC_{1-4}alkyl group);

h) (to prepare a compound of formula I wherein R_4 denotes an optionally phenyl-substituted C_{1-2}-alkyl group) alkylating a compound of formula I (wherein R_4 is a hydrogen atom);

i) performing the process of any one of steps (a) to (h) above on a reagent having a protecting group and subsequently removing the protecting group used;

j) converting a compound of formula I into a salt thereof; and

k) resolving a compound of formula I into its isomers.

The hydrolysis of step (a) is appropriately carried out either in the presence of an acid such as hydrochloric acid, sulphuric acid, phosphoric acid, acetic acid, acetic acid/hydrochloric acid, trichloroacetic acid or trifluoroacetic acid, or in the presence of a base such as lithium hydroxide, sodium hydroxide or potassium hydroxide in a suitable solvent such as water, methanol, water/methanol, ethanol, water/ethanol, water/isopropanol, water/tetrahydrofuran or water/dioxane, at temperatures between -10°C and 120°C, e.g. at temperatures between ambient temperature and the boiling temperature of the reaction mixture. Upon treatment with an organic acid such as trichloroacetic acid or trifluoroacetic acid, any alcoholic hydroxy groups present may simultaneously be converted into a corresponding acyloxy group, such as a trifluoroacetoxy group.

During acid hydrolysis, depending on the conditions used, other hydrolytically cleavable groups present in a compound of formula II, such as the acetyl,

trifluoroacetyl, benzoyl, tert.butyloxycarbonyl or benzyloxycarbonyl group may be simultaneously cleaved.

If a compound of formula II contains, for example, a tert.butyloxycarbonyl group, the tert.butyl group may also be cleaved by treating with an acid such as trifluoroacetic acid, hydrochloric acid, formic acid, p-toluenesulphonic acid, sulphuric acid, phosphoric acid or polyphosphoric acid, optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran or dioxane, preferably at temperatures between -10°C and 120°C, e.g. at temperatures between 0 and 60°C, or thermally, optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran or dioxane and optionally in the presence of a catalytic amount of an acid such as p-toluenesulphonic acid, sulphuric acid, phosphoric acid or polyphosphoric acid, preferably at the boiling temperature of the solvent used, e.g. at temperatures between 40°C and 100°C.

If a compound of formula II contains, for example, a benzyloxycarbonyl group, the benzyl group may also be hydrogenolytically cleaved in the presence of a hydrogenation catalyst such as palladium/charcoal, in a suitable solvent such as methanol, ethanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxane or dimethylformamide, preferably at temperatures between 0 and 50°C, e.g. at ambient temperature, under a hydrogen pressure of 1 to 10 bar. During hydrogenolysis, other groups may also be reduced at the same time, e.g. a nitro group may be reduced to an amino group or a benzyloxy group to a hydroxy group, or a benzylamino group into an amino group. Furthermore, C=C double bonds may simultaneously be hydrogenated into single bonds.

The reaction of step (b) is preferably carried out in a suitable solvent, optionally in the presence of a base or optionally in the presence of an acid activating agent or in the presence of a reducing agent at temperatures between -30 and 150°C.

If Z_1 denotes a nucleophilic leaving group, the reaction of step (b) is conveniently carried out in a solvent or mixture of solvents such as water, tetrahydrofuran, tetrahydrofuran/water, dioxane, dioxane/water, methylene chloride, chloroform, ethyl acetate or dimethylformamide, conveniently in the presence of a base such as sodium carbonate, potassium carbonate or sodium hydroxide solution or in the presence of a tertiary organic base such as triethylamine, N-ethyl-diisopropylamine, N-methyl-morpholine or pyridine, which may simultaneously be used as solvent, optionally in the presence of a reaction accelerator such as potassium iodide at temperatures between -30 and 100°C, but preferably at temperatures between -10 and 80°C.

If Z_1 denotes a hydroxy group, the reaction of step (b) is conveniently carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, optionally in the presence of an acid such as hydrochloric acid or in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionylchloride, trimethylchlorosilane, hydrochloric acid, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, 2-(1H-benzotriazolyl)-1,1,3,3-tetramethyl-uronium salts, N,N'-carbonyldiimidazole, N,N'-thionyldiimidazole or triphenylphosphine/carbon tetrachloride, optionally in

the presence of dimethylaminopyridine or 1-hydroxy-benzotriazole, appropriately at temperatures between 0 and 150°C, preferably at temperatures between 0 and 50°C.

If Z_1 together with an adjacent hydrogen atom of the group R_b denotes an oxygen atom, the reductive alkylation of step (b) is conveniently carried out in a suitable solvent such as methanol, ethanol, tetrahydrofuran, dioxane, acetonitrile or mixtures thereof with water, in the presence of a suitable reducing agent such as formic acid or a suitable complex metal hydride, but preferably in the presence of sodium cyanoborohydride, or with hydrogen in the presence of a hydrogenation catalyst such as palladium/charcoal, at temperatures between 0 and 50°C, but preferably at ambient temperature.

If Z_2 denotes a halogen atom or a sulphonyloxy group substituted at the sulphonyl group, the reaction of step (c) is expediently carried out in a solvent such as tetrahydrofuran, dioxane, methylene chloride, chloroform, ethyl acetate, dimethylsulphoxide or dimethylformamide, appropriately in the presence of a base such as sodium carbonate, potassium carbonate or sodium hydroxide solution or in the presence of a tertiary organic base such as triethylamine, N-ethyl-diisopropylamine or N-methyl-morpholine, which may simultaneously serve as solvent, optionally in the presence of a reaction accelerator such as potassium iodide, at temperatures between -30 and 100°C, but preferably at temperatures between -10 and 80°C.

If Z_2 denotes a hydroxy group, the reaction of step (c) is preferably carried out using the compound of formula VI as solvent, in the presence of thionylchloride or an acid such as hydrochloric acid or sulphuric acid, at temperatures between -10°C and 100°C, preferably at

temperatures between 0°C and 50°C.

The reduction of step (d) is preferably carried out in a suitable solvent such as methanol, methanol/water, methanol/ammonia, methanol/water/ammonia, methanol/hydrochloric acid, methanol/ethereal hydrochloric acid, ethanol, ethyl acetate, ether, tetrahydrofuran, dioxane, dimethylformamide or glacial acetic acid, in the presence of catalytically activated hydrogen, e.g. hydrogen in the presence of Raney nickel, platinum or palladium/charcoal, or in the presence of a metal hydride such as sodium borohydride, sodium cyanoborohydride or lithium borohydride, at temperatures between -20°C and 100°C, preferably at temperatures between 0°C and 60°C.

The reaction of step (e) is conveniently carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, dimethylsulphoxide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, optionally in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionylchloride, trimethylchlorosilane, hydrochloric acid, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, 2-(1H-benzotriazolyl)-1,1,3,3-tetramethyl-uronium salts, N,N'-carbonyldiimidazole, N,N'-thionyldiimidazole or triphenylphosphine/carbon tetrachloride, optionally in the presence of dimethylaminopyridine or 1-hydroxy-benzotriazole and/or a base such as triethylamine, N-ethyl-diisopropylamine or N-methyl-morpholine, conveniently at temperatures between -10 and 150°C, preferably at temperatures between 0 and 50°C.

The reaction of step (f) is conveniently carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, dimethylsulphoxide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, optionally in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionylchloride, trimethylchlorosilane, hydrochloric acid, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, 2-(1H-benzotriazolyl)-1,1,3,3-tetramethyl-uronium salts, N,N'-carbonyldiimidazole, N,N'-thionyldiimidazole or triphenylphosphine/carbon tetrachloride, optionally in the presence of dimethylaminopyridine or 1-hydroxy-benzotriazole and/or a base such as triethylamine, N-ethyl-diisopropylamine or N-methyl-morpholine, conveniently at temperatures between -10 and 150°C, preferably at temperatures between 0 and 50°C.

The reduction of step (g) is preferably carried out in a suitable solvent such as methanol, methanol/water, methanol/water/ammonia, ethanol, ether, tetrahydrofuran, dioxane or dimethylformamide, optionally with the addition of an acid such as hydrochloric acid, in the presence of catalytically activated hydrogen, e.g. hydrogen in the presence of Raney nickel, platinum or palladium/charcoal, or in the presence of a metal hydride such as sodium borohydride, lithium borohydride or lithium aluminium hydride, at temperatures between 0 and 100°C, preferably at temperatures between 20 and 80°C.

The alkylation of step (h) is conveniently carried out with a suitable halide such as methyliodide, ethylbromide, benzylchloride or phenylethylbromide,

preferably in a solvent such as methylene chloride, tetrahydrofuran, dioxane, dimethylsulphoxide or dimethylformamide, optionally in the presence of a base such as sodium carbonate, potassium carbonate or sodium hydroxide solution or in the presence of a tertiary organic base such as N-ethyl-diisopropylamine or N-methyl-morpholine, which may simultaneously be used as solvent, at temperatures between -30 and 100°C, but preferably at temperatures between -10 and 80°C.

During the reactions described hereinbefore, reactive groups such as hydroxy, carboxy, amino, alkylamino or imino groups may be protected by means of conventional protecting groups which are removed by cleaving after the reaction.

For example, the protective group for a hydroxy group may be a trimethylsilyl, acetyl, benzoyl, tert.butyl, trityl, benzyl or tetrahydropyranyl group, the protecting group for a carboxyl group may be a trimethylsilyl, methyl, ethyl, tert.butyl, benzyl or tetrahydropyranyl group, and the protecting group for an amino, alkylamino or imino group may be an acetyl, trifluoroacetyl, benzoyl, ethoxycarbonyl, tert.-butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl or 2,4-dimethoxybenzyl group and for the amino group a phthalyl group may also be considered.

The optional subsequent cleaving of a protecting group may, for example, be carried out hydrolytically in an aqueous solvent, e.g. in water, isopropanol/water, tetrahydrofuran/water or dioxane/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulphuric acid or in the presence of an alkali metal base such as lithium hydroxide, sodium hydroxide or potassium hydroxide or by ether cleaving, e.g. in the presence of iodotrimethylsilane, at temperatures between

0 and 100°C, preferably at temperatures between 10 and 50°C.

However, a benzyl, methoxybenzyl or benzyloxycarbonyl group may for example be cleaved hydrogenolytically, eg. using hydrogen in the presence of a catalyst such as palladium/charcoal in a solvent such as methanol, ethanol, ethyl acetate, dimethylformamide, dimethylformamide/acetone or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid, at temperatures between 0 and 50°C, but preferably at ambient temperature, under a hydrogen pressure of 1 to 7 bar, preferably 3 to 5 bar. During hydrogenolytic cleaving of benzyl groups, any C=C-double bonds present in a compound of formula II may simultaneously be hydrogenated. For example, an N-benzyl-dehydro-piperidyl group may be converted into a piperidyl group in this way.

A methoxybenzyl group may also be cleaved in the presence of an oxidising agent such as cerium(IV)-ammonium nitrate, in a solvent such as methylene chloride, acetonitrile or acetonitrile/water, at temperatures between 0 and 50°C, but preferably at ambient temperature.

A 2,4-dimethoxybenzyl group, however, is preferably cleaved in trifluoroacetic acid in the presence of anisole.

A tert.butyl or tert.butyloxycarbonyl group is preferably cleaved by treating with an acid such as trifluoroacetic acid or hydrochloric acid, optionally using a solvent such as methylene chloride, dioxane, ether or dioxane/ether.

A phthalyl group is preferably cleaved in the presence of hydrazine or a primary amine such as methylamine, ethylamine or n-butylamine in a solvent such as methanol, ethanol, isopropanol, toluene/water or dioxane, at temperatures between 20 and 50°C.

An allyloxycarbonyl group is cleaved by treating with a catalytic amount of tetrakis-(triphenylphosphine)-palladium(0), preferably in a solvent such as tetrahydrofuran and preferably in the presence of an excess of an allyl group acceptor such as morpholine or 1,3-dimedone, at temperatures between 0 and 100°C, preferably at ambient temperature and under inert gas, or by treating with a catalytic amount of tris-(triphenylphosphine)-rhodium(I)chloride, in a solvent such as aqueous ethanol and optionally in the presence of a base such as 1,4-diazabicyclo[2.2.2]octane, at temperatures between 20 and 70°C.

Furthermore, the compounds of formula I obtained may be resolved into their enantiomers and/or diastereomers.

Thus, for example, the cis/trans mixtures obtained may be resolved by chromatography into the cis and trans isomers thereof and the compounds of formula I which occur in racemate form may be separated by conventional methods (see Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes, and compounds of formula I having at least 2 stereogenic centres may be separated on the basis of their physical-chemical differences using known methods, e.g. by chromatography and/or fractional crystallisation, into the diastereomers thereof, which, if they occur in racemic form, may subsequently be separated into the enantiomers as mentioned above.

The separation of enantiomers is preferably effected by column separation on chiral phases or by recrystallisation from an optically active solvent or by reaction with optically active substances (especially acids and the activated derivatives thereof or alcohols), which form salts or derivatives such as esters or amides with the racemic compound, and separation of the diasteromeric salt mixture or derivative thus obtained, e.g. on the basis of their different solubilities, whilst the free antipodes may be released from the pure diastereomeric salts by the action of suitable agents. Particularly useful, optically active acids include, for example, the D- and L-forms of tartaric acid, and dibenzoyltartaric acid, di-o-tolyl tartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, aspartic acid and quinic acid. Examples of optically active alcohols include for example (+)- or (-)-menthol and examples of optically active acyl groups in amides include, for example, (+)- or (-)-menthyloxycarbonyl.

Moreover, the compounds of formula I obtained may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts thereof with inorganic or organic acids. Examples of suitable acids include hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid.

In addition, the compounds of formula I thus obtained, if they contain a carboxyl group, may subsequently, if desired, be converted into the addition salts thereof with inorganic or organic bases, more particularly, for pharmaceutical use, into the physiologically acceptable addition salts thereof. Examples of suitable bases include sodium hydroxide, potassium hydroxide, ammonia,

cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

The starting compounds used in the process of the invention are known or may be obtained by conventional techniques (see Examples I to XXIV).

As mentioned above, the compounds of the invention have valuable properties. Thus, the compounds of formula I, wherein A represents an aminoalkyl, aza- or diazacycloalkyl group optionally substituted at the nitrogen, or represents a pyridyl or quinuclidinyl group or a group which may optionally be converted <u>in vivo</u> into an aminoalkyl, aza- or diazacycloalkyl group, e.g. an amino, aza- or diazacycloalkyl group substituted at the nitrogen by an alkoxycarbonyl, alkenyloxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, trifluoromethylcarbonyl, alkanoyloxymethoxycarbonyl, cycloalkanoyloxymethoxy-carbonyl or aralkanoyloxymethoxycarbonyl group and $-COOR_a$ denotes a carboxyl group or a group which may be converted <u>in vivo</u> into a carboxyl group, e.g. an alkoxy, alkenyloxy, phenylalkoxy, cycloalkyloxy, alkanoyloxyalkoxy, cycloalkanoyloxyalkoxy, phenylalkanoyloxyalkoxy, benzoyloxyalkoxy, alkoxycarbonyloxyalkoxy or cycloalkyloxycarbonyloxy-alkoxycarbonyl group, have valuable pharmacological properties, and in addition to having an inhibitory effect on inflammation and bone degradation, they have in particular antithrombotic, antiaggregatory and tumour- or metastasis-inhibiting effects.

Viewed from a further aspect the invention thus provides a pharmaceutical composition comprising a compound of formula I or a physiologically acceptable salt thereof together with at least one physiologically acceptable carrier or excipient.

Viewed from a still further aspect the invention also provides the use of a compound of formula I or a physiologically acceptable salt thereof, for the manufacture of a medicament for use in combating inflammation, bone degradation, tumours, metastases, thrombosis and aggregation-related conditions.

Viewed from a yet still further aspect the invention provides a method of treatment of the human or non-human, preferably mammalian body to combat inflammation, bone degradation, tumours, metastases, thrombosis and aggregation-related conditions, said method comprising administering to said body a compound of formula I or a physiologically acceptable salt thereof.

By way of example, the biological activity of the compounds according to the invention were investigated as follows:

1. Competitive binding of ^{3}H-BIBU 52/test substance to human thrombocytes:

A suspension of human thrombocytes in plasma is incubated with ^{3}H-BIBU 52 [^{3}H-BIBU 52, which is disclosed in DE-A-4214245 is (3S,5S)-5-[(4'-amidino-4-biphenylyl)oxymethyl]-3-[(carboxyl)methyl]-2-pyrrolidinone[3-^{3}H-4-biphenylyl] and is used in place of the conventional ^{125}I fibrinogen ligand] and various concentrations of the test substance. The free and bound ligand are separated by centrifuging and quantified by scintillation counting. The inhibition of ^{3}H-BIBU 52 binding by the test substance is determined from the measurements obtained.

In order to do this, donor blood is taken from an anticubital vein and anticoagulated with trisodium citrate (final concentration 13 mM). The blood is centrifuged for 10 minutes at 170 x g and the supernatant platelet-rich plasma (PRP) is removed. The remaining blood is vigorously centrifuged once more in order to obtain plasma. The PRP is diluted 1:10 with autologous plasma. 750 µl are incubated with 50 µl of physiological saline solution, 100 µl of test substance solution, 50 µl of ^{14}C-sucrose (3,700 Bq) and 50 µl of ^{3}H-BIBU 52 (final concentration: 5 nM) at ambient temperature for 20 minutes. In order to measure the non-specific binding, 5 µl of BIBU 52 (final concentration: 30 µM) are used in place of the test substance. The samples are centrifuged for 20 seconds at 10,000 x g and the supernatant is poured off. 100 µl thereof are measured in order to determine the free ligand. The pellet is dissolved in 500 µl of 0.2N NaOH, 450 µl are mixed with 2 ml of scintillator and 25 µl of 5N HCl and measured. The residual plasma remaining in the pellet is determined from the ^{14}C-content and the bound ligand is determined from the ^{3}H-measurement.

After the non-specific binding has been deducted, the pellet activity is plotted against the concentration of the test substance and the concentration for a 50% inhibition of binding is determined.

2. Antithrombotic activity

Method

Thrombocyte aggregation is measured using the method of Born and Cross (J. Physiol. 170: 397 (1964)) in platelet-rich plasma taken from healthy volunteers. To inhibit coagulation, the blood is mixed with 3.14% sodium citrate in a volume ratio of 1:10.

Collagen-induced aggregation

The pattern of the decrease in optical density of the platelet suspension is photometrically measured and recorded after the addition of the aggregation-triggering substance. The rate of aggregation is determined from the angle of inclination of the density curve. The point on the curve where there is maximum light transmittance is used to calculate the optical density.

The concentration of collagen used is as small as possible but sufficient to produce an irreversible reaction curve. Standard commercial collagen produced by Hormonchemie of Munich is used. Before the addition of the collagen the plasma is incubated for 10 minutes with the substance at 37°C.

From the concentration/activity curve the EC_{50} is determined, which indicates the concentration giving a 50% change in the optical density in terms of the inhibition of aggregation.

The following table shows the results which were obtained:

Substance (Example No.)	Competitive binding of ^{3}H-BIBU 52/test substance to human thrombocytes IC_{50} [nM]	Inhibition of platelet aggregation EC_{50} [nM]
2	1 100	840
2.1	>100 000	3 300
2.2	4 500	3 300
3	190	260
3.1	1 400	2 400
3.3	17	260
3.4	2 000	5 800
3.6	14	120
5	2 900	5 600

The inhibition of thrombocyte aggregation after oral administration of the test substance is determined ex vivo on Rhesus monkeys.

Directly before the oral administration of the test substance suspended in Natrosol, a blood sample is taken from the cubital vein of the animals to provide a reference value. At specified times after the administration of the substance, fresh blood samples are taken and investigated as follows.

Whole blood, mixed with 3.14% sodium citrate in a ratio by volume of 1:10 is centrifuged at 200 x g for 15 minutes. The supernatant, platelet-rich plasma, is carefully removed. From the sediment which is rich in erythrocytes, the platelet-depleted plasma is obtained as supernatant, by centrifuging at 4000 x g for 10

minutes.

The thrombocyte aggregation triggered with collagen (Hormonchemie, Munich; 2 µg/ml final concentration in platelet-rich plasma) in these ex vivo samples is measured photometrically using the method of Born and Cross (J. Physiol. 170: 397 (1964)). The maximum light transmittance of the platelet-rich plasma, measured after collagen stimulation, is compared with the reference value in order to determine the inhibition of aggregation at the various times of blood sampling after the administration of the substance, relative to the reference value.

The compounds of Examples 2 and 5(2) inhibit the collagen-induced thrombocyte aggregation ex vivo for more than 2 hours after the oral administration of 1 mg/kg.

The compounds according to the invention are well tolerated because after intravenous administration of 30 mg/kg of the compounds of Examples 2 and 3 to three mice in each case, no animals died.

In the light of their inhibitory effect on cell-cell or cell-matrix interactions, the compounds of formula I and the physiologically acceptable addition salts thereof are suitable for combating or preventing diseases in which smaller or greater cell aggregates occur or in which cell-matrix interactions play a part, e.g. in treating or preventing venous and arterial thrombosis, cerebrovascular diseases, lung embolism, cardiac infarction, arteriosclerosis, osteoporosis and the metastasis of tumours and the treatment of genetically caused or acquired disorders of cell interactions with one another or with solid structures. They are also suitable for parallel therapy in thrombolysis with

fibrinolytics or vascular interventions such as transluminal angioplasty or in the treatment of shock, psoriasis, diabetes and inflammation.

For treating or preventing the diseases mentioned above, the dosage is between 0.1 μg and 30 mg/kg of body weight, preferably 1 μg to 15 mg/kg of body weight, given in up to 4 doses per day. For this purpose the compounds of the invention, optionally in conjunction with other active substances such as thromboxane receptor antagonists and thromboxane synthesis inhibitors or combinations thereof, serotonin antagonists, α-receptor antagonists, alkylnitrates such as glycerol trinitrate, phospho-diesterase inhibitors, prostacyclin and the analogues thereof, fibrinolytics such as tPA, prourokinase, urokinase, streptokinase, or anticoagulants such as heparin, dermatane sulphate, activated protein C, vitamin K antagonists, hirudine, inhibitors of thrombin or other activated clotting factors, may be incorporated together with one or more inert conventional carriers and/or diluents, e.g. corn starch, lactose, sucrose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethyleneglycol, propyleneglycol, stearylalcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof, into conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions, solutions, sprays or suppositories.

The following Examples are provided to illustrate the invention in a non-limiting fashion. Percentages and ratios are by weight unless otherwise indicated except eluant ratios which are by volume:

Preparation of the starting compounds:

Example I

4-(4-Carboxyphenyl)-piperidine-hydrochloride

157.4 g of oxalylchloride are added dropwise to a solution of 63.0 g of 1-acetyl-4-phenyl-piperidine in 1000 ml of methylene chloride, with thorough stirring, at -10 to -20°C. Then 46.7 g of aluminium chloride are added. The mixture is stirred for 1 hour at -10°C and a further 82.7 g of aluminium chloride are added. After another 2 hours the cooling bath is removed and the mixture is stirred for 24 hours at ambient temperature. The reaction solution is carefully stirred into about 4 litres of ice/water and the aqueous phase is extracted twice with methylene chloride. The combined organic phases are washed with water, dried over sodium sulphate and the solvent is removed under reduced pressure. The residue remaining is dissolved in 2.5 litres of 2N sodium hydroxide solution with vigorous stirring. Ice is added to the dark aqueous solution and it is acidified with conc. hydrochloric acid. The precipitate is suction filtered, washed with water and refluxed for 5 hours in 2 litres of 6N hydrochloric acid. The solvent is removed under reduced pressure. The solid remaining is triturated with a little water and suction filtered.

Yield: 40.5 g (54% of theory),

Melting point: > 300°C

R_f value: 0.07 (silica gel; methylene chloride/methanol/conc. ammonia = 4:1:0.25)

Example II

1-tert.Butyloxycarbonyl-4-(4-carboxyphenyl)-piperidine

47.5 g of 4-(4-carboxyphenyl)-piperidine-hydrochloride are carefully added to 16.4 g of sodium hydroxide in 300 ml of water. The suspension is diluted with 500 ml of dioxane and 250 ml of water. Then 54.6 g of di-tert.butyl pyrocarbonate are added in batches. The mixture is stirred for 16 hours at ambient temperature. The precipitate is suction filtered and the filtrate is partially concentrated by evaporation under reduced pressure. The precipitate and the remaining aqueous filtrate are combined and diluted with 1 litre of water. The aqueous phase is adjusted to pH 2 using saturated potassium hydrogen sulphate solution and extracted twice with ethyl acetate. The combined ethyl acetate phases are washed with saturated saline solution, dried over sodium sulphate and the solvent is removed under reduced pressure. The crude crystalline product is triturated with a little ethyl acetate, suction filtered and dried.
Yield: 54.0 g (90% of theory),
Melting point: 172-174°C
R_f value: 0.73 (silica gel; ethyl acetate/cyclohexane = 4:1)

Example III

Methyl 3-(4-aminophenyl)-2-(n-butylsulphonylamino)-propionate

19 g of methyl 2-(n-butanesulphonylamino)-3-(4-nitrophenyl)-propionate in 200 ml of ethyl acetate are treated with hydrogen at 5 bars pressure in the presence of 2 g of 10% palladium/charcoal for 1.5 hours at ambient temperature. The catalyst is filtered off, the filtrate is evaporated down and the residue is used

without further purification.
Yield: 17.8 g (100% of theory),
R_f value: 0.43 (silica gel; cyclohexane/ethyl acetate = 1:1)

The following compound is obtained analogously:

(1) Methyl 3-(4-amino-phenyl)-propionate
Methyl 4-nitro-cinnamate, hydrogenated at 50°C.
R_f value: 0.76 (silica gel; cyclohexane/ethyl acetate = 1:3)

Example IV

Methyl 2-(n-butanesulphonylamino)-3-(4-nitrophenyl)-propionate

25.9 g of methyl 2-amino-3-(4-nitrophenyl)-propionate hydrochloride are suspended in 100 ml of methylene chloride and mixed with 32 g of N-ethyl-diisopropylamine, whereupon the precipitate dissolves. To the solution are added dropwise, at 8 to 15°C, 17.1 g of n-butanesulphonylchloride in 20 ml of methylene chloride. After stirring for 16 hours at ambient temperature, 10 g of N-ethyl-diisopropylamine are added whilst cooling with ice and a further 8 g of n-butanesulphonylchloride are added dropwise and stirred for a further 2 hours at ambient temperature. The mixture is combined with ice water, the organic phase is washed successively with water, 1N hydrochloric acid and water and concentrated by evaporation. The residue is purified over silica gel (eluant: methylene chloride).
Yield: 19.4 g (57% of theory),
Melting point: 100-102°C
R_f value: 0.38 (silica gel; cyclohexane/ethyl acetate = 6:4)

Example V

Methyl 2-amino-3-(4-nitrophenyl)-propionate-hydrochloride

21 g of 4-nitro-phenylalanine are suspended in 250 ml of methanol and mixed with 10 ml of methanolic hydrochloric acid, whereupon the solid product dissolves. The mixture is left to stand for 60 hours at ambient temperature and evaporated down in vacuo. The product is used without any further purification.
Yield: 25.9 g (99% of theory),
Melting point: 206-208°C (decomp.)
R_f value: 0.67 (Reversed Phase Plate RP8; methanol/5% sodium chloride solution = 6:4)

The following compound is obtained analogously:

(1) Methyl 3-(trans-4-amino-cyclohexyl)-propionate-hydrochloride
Melting point: above 200°C

Example VI

3-(trans-4-Amino-cyclohexyl)-propionic acid-hydrochloride

26 g of 3-(trans-4-acetamino-cyclohexyl)-propionic acid are refluxed for 16 hours in 200 ml of 6N hydrochloric acid. The mixture is evaporated to dryness in vacuo and evaporated down several more times after the addition of toluene and methanol. The residue is used directly.
Yield: 26 g (100% of theory)

Example VII

3-(trans-4-Acetaminocyclohexyl)-propionic acid

112.7 g of 3-(4-acetaminophenyl)-propionic acid and 10 g of platinum dioxide are treated in 350 ml of glacial acetic acid at 60°C with hydrogen at 5 bars pressure. After 1.5 and 7 hours, the platinum dioxide is replaced with fresh. The entire reaction time is 10 hours. The mixture is evaporated to dryness in vacuo and the residue is recrystallised from 1800 ml of acetone. The primary crystals are also recrystallised from 50 ml of 80% acetic acid.

Yield: 26 g (22.4% of theory),

Melting point: 200-201°C

R_f value: 0.30 (silica gel; methylene chloride/ethyl acetate/glacial acetic acid = 4:1:0.4)

After evaporation and recrystallisation from 100 ml of water, 53.6 g (46% of theory) of cis-3-(4-acetamino-cyclohexyl)-propionic acid are obtained from the acetone mother liquor.

Example VIII

1-Benzyl-4-(3-carboxyphenyl)-3,4-dehydro-piperidine-hydrochloride

25 g of 1-benzyl-4-(3-bromo-phenyl)-3,4-dehydro-piperidine are dissolved in 300 ml of tetrahydrofuran. The mixture is cooled to below -65°C and at this temperature, within 30 minutes, 47.6 ml of a 1.6 molar solution of n-butyllithium in hexane are added dropwise. The resulting mixture is stirred for a further hour and then a slow stream of carbon dioxide dried over conc. sulphuric acid is passed over the reaction solution. The temperature is first maintained for 1 hour at below -65°C and then slowly allowed to rise to ambient

temperature and the reaction mixture is left to stand at this temperature for 60 hours. It is then evaporated to dryness, the residue is taken up in 500 ml of ethyl acetate and extracted with water. The aqueous phases are concentrated by evaporation in vacuo, cooled in an ice bath and adjusted to pH 1 using 2N hydrochloric acid. The precipitated crystals are filtered off and washed with water.

Yield: 9 g (40% of theory),

Melting point: from 185°C (decomp.)

R_f value: 0.50 (Reversed Phase Plate RP8; methanol/5% sodium chloride solution = 6:4)

Example IX

1-Benzyl-4-(3-bromophenyl)-3,4-dehydro-piperidine

29.6 g of 1-benzyl-4-(3-bromophenyl)-4-hydroxy-piperidine, 32.5 g of p-toluenesulphonic acid hydrate and 300 ml of toluene are heated for 2 hours using a water separator. After cooling, the mixture is diluted with methylene chloride, ice water is added and the resulting mixture is made alkaline with 30% sodium hydroxide solution. The aqueous phase is extracted once again with methylene chloride and the combined organic phases are evaporated down in vacuo.

Yield: 25.2 g (90% of theory),

R_f value: 0.69 (silica gel; methylene chloride/methanol = 100:2)

Example X

1-Benzyl-4-(3-bromophenyl)-4-hydroxy-piperidine

To a solution of 35.7 g of 1,3-dibromo-benzene in 200 ml of ether, 93.1 ml of a 1.6 molar solution of n-

butyllithium in hexane are added dropwise over 25 minutes at a temperature below 0°C. The mixture is stirred for a further 40 minutes and then, at a temperature below 10°C, a solution of 28.2 g of freshly distilled 1-benzyl-4-piperidone in 40 ml of ether is added dropwise. The mixture is stirred for a further 30 minutes at this temperature and finally for 1 hour at ambient temperature. 500 ml of saturated saline solution are added, the aqueous phase is extracted twice more with ethyl acetate, the organic phases are evaporated down in vacuo and the residue is purified by column chromatography over silica gel (eluant: methylene chloride/methanol = 100:2)

Yield: 29.6 g (56% of theory),

R_f value: 0.34 (silica gel; methylene chloride/methanol = 100:2)

Example XI

3-(4-Acetaminophenyl)-propionic acid

155 g of methyl 3-(4-acetaminophenyl)-propionate are dissolved in 1000 ml of methanol, heated to 50°C and mixed with 700 ml of 2N sodium hydroxide solution. The mixture is cooled to ambient temperature and stirred for another 3 hours. It is then cooled in an ice bath, 750 ml of 2N hydrochloric acid are added and the mixture is stirred for another hour whilst cooling with ice. The precipitate is filtered off and washed with a little ice water.

Yield: 112.7 g (77.6% of theory),

Melting point: 144-147°C

R_f value: 0.25 (silica gel; methylene chloride/ethyl acetate/glacial acetic acid = 8:1:0.4)

Example XII

Methyl 3-(4-acetaminophenyl)-propionate

138.4 g of methyl 3-(4-aminophenyl)-propionate are dissolved in 1000 ml of methylene chloride and 119 ml of triethylamine are added. The mixture is cooled to below 0°C and within 35 minutes at 0 to 10°C a solution of 58 ml of acetylchloride in 200 ml of methylene chloride is added dropwise. The resulting mixture is stirred for one hour at 0°C, 300 ml of water are added, the organic phase is extracted twice more with water and evaporated down in vacuo.

Yield: 155.5 g (91% of theory),

Melting point: 118-120°C

R_f value: 0.50 (silica gel; cyclohexane/ethyl acetate = 1:3)

Example XIII

4-[4-[[4-[2-(Methoxycarbonyl)-ethyl]-phenyl]-iminomethyl]-phenyl]-1-trifluoroacetyl-piperidine

6.9 g of 4-(4-formylphenyl)-1-trifluoroacetyl-piperidine and 4.33 g of methyl 3-(4-aminophenyl)-propionate are refluxed for 5 hours in 50 ml of toluene using a water separator. The mixture is evaporated down in vacuo and the product is used without any further purification.

Yield: 10.8 g (100% of theory),

R_f value: 0.43 (silica gel; cyclohexane/ethyl acetate = 2:1)

Example XIV

4-(4-Formylphenyl)-1-trifluoroacetyl-piperidine

To a solution of 8.3 g of 4-phenyl-1-trifluoroacetyl-piperidine in 30 ml of methylene chloride, 7.8 ml of titanium tetrachloride are added dropwise at a temperature below 0°C. After 10 minutes, 3.5 ml of dichloromethylmethylether are added dropwise over 40 minutes whilst the temperature is maintained below 0°C. The mixture is left to stand for 16 hours at ambient temperature, poured onto ice water and the aqueous phase is extracted several times with methylene chloride. The organic phases are evaporated down in vacuo and the residue is purified by column chromatography over silica gel (eluant: cyclohexane/ethyl acetate = 2:1)
Yield: 6.9 g (75% of theory),
Melting point: 76-77°C
R_f value: 0.42 (silica gel; cyclohexane/ethyl acetate = 2:1)

Example XV

4-Phenyl-1-trifluoroacetyl-piperidine

25 g of 4-phenyl-piperidine are dissolved in 250 ml of methylene chloride, 29.8 ml of N-ethyl-diisopropylamine are added and the mixture is cooled to 0°C. 24.1 ml of trifluoroacetic acid anhydride are added dropwise to the solution so that the temperature does not exceed 10°C. It is stirred for a further 30 minutes at 0°C, allowed to warm to ambient temperature, 100 ml of water are added and the organic phase is washed twice more with water. The methylene chloride phase is evaporated down and the residue is used without further purification.
Yield: 40 g (100% of theory),

R_f value: 0.90 (silica gel; cyclohexane/ethyl acetate = 1:1)

Example XVI

4-(4-Aminophenyl)-1-trifluoroacetyl-piperidine

a) 4-Phenyl-1-trifluoroacetyl-piperidine

To a solution of 125 g (0.775 Mol) of 4-phenyl-piperidine and 149 ml (0.775 Mol) of N,N-diisopropyl-ethylamine in 1300 ml of dichloromethane, 120.5 ml (0.775 Mol) of trifluoroacetic acid anhydride are added dropwise at 5°C, with stirring, over a period of 2 hours. The mixture is then stirred for a further hour whilst cooling with ice, left to stand overnight at ambient temperature and then diluted with 400 ml of water. The dichloromethane phase is separated off, washed twice with 400 ml of water, dried over sodium sulphate and evaporated to dryness in vacuo.

Yield: 193 g (97% of theory)

Yellow crystals

R_f value: 0.88 (silica gel; cyclohexane/ethyl acetate = 1:1)

b) 4-(4-Nitrophenyl)-1-trifluoroacetyl-piperidine

80 g (0.311 Mol) of the 4-phenyl-1-trifluoroacetyl-piperidine obtained in a) are dissolved in a mixture of 400 ml of glacial acetic acid and 200 ml of acetic anhydride. This solution is cooled to 10°C in an ice bath and 1.6 g of sodium nitrite are added, with stirring, followed by the dropwise addition of 51.9 ml (0.311 Mol) of fuming nitric acid. The mixture is left to stand overnight at ambient temperature and then poured onto 1000 ml of water which contains 200 g of ice. The pH is adjusted to 8 using 8N sodium hydroxide solution within 4.5 hours, with cooling to prevent the

temperature exceeding 20°C. The mixture is extracted with a total of 2000 ml of dichloromethane, the combined dichloromethane extracts are washed with 100 ml of 0.1 N sodium hydroxide solution and then twice with water, dried over sodium sulphate and evaporated to dryness in vacuo. The residue is crystallised from ethyl acetate/cyclohexane.
Yield: 54.5 g (58% of theory)
Yellow crystals
Melting point: 100-102°C

c) 4-(4-Aminophenyl)-1-trifluoroacetyl-piperidine
The compound prepared in b) is dissolved in 700 ml of ethyl acetate and, after the addition of 7 g of palladium on charcoal (10%), it is hydrogenated at ambient temperature under 3 bars of hydrogen pressure. The catalyst is filtered off and the ethyl acetate solution is evaporated to dryness in vacuo.
Yield: 39.7 g (quantitative)
R_f value: 0.25 (silica gel; cyclohexane:ethyl acetate = 1:1)

Example XVII

1-tert.Butyloxycarbonyl-4-[4-[[4-[2-(methoxycarbonyl)-ethyl]-piperidino]-methyl]-phenyl]-piperidine

a) 1-tert.Butyloxycarbonyl-4-(4-hydroxymethyl-phenyl)-piperidine
To a solution of 5 g (0.0164 Mol) of 1-tert.butyloxycarbonyl-4-(4-carboxy-phenyl)-piperidine and 1.66 g (0.0164 Mol = 2.28 ml) of triethylamine in 100 ml of tetrahydrofuran, a solution of 1.78 g (0.0164 Mol = 1.57) ml of ethylchloroformate in 10 ml of tetrahydrofuran is added dropwise with stirring at 5°C and the mixture is stirred at this temperature for a

further hour. The triethylamine-hydrochloride precipitated is then suction filtered and washed with tetrahydrofuran. The combined tetrahydrofuran phases are then added dropwise, with stirring at 10 to 15°C, into a solution of 1.55 g (0.041 Mol) of sodium borohydride. After stirring overnight at ambient temperature the mixture is evaporated to dryness in vacuo. The residue remaining is distributed between ethyl acetate and 1N sodium hydroxide solution. The ethyl acetate phase is washed with water, dried over sodium sulphate and evaporated to dryness in vacuo. The residue remaining is crystallised from petroleum ether.
Yield: 4.05 g (84.7% of theory),
Melting point: 78-80°C

b) 1-tert.Butyloxycarbonyl-4-(4-chloromethylphenyl)-piperidine

A solution of 3.95 g (0.0136 Mol) of compound a) and 2.74 g (0.0271 Mol = 3.8 ml) of triethylamine in 80 ml of dichloromethane are slowly combined, with stirring, with 3.1 g (0.0271 Mol = 2.1 ml) of mesylchloride. After addition is complete the mixture is left to stand overnight and the clear solution is then evaporated to dryness. The residue remaining is chromatographed over silica gel using dichloromethane as eluant.
Yield: 3.75 g (89% of theory),
Melting point: 56-58°C
R_f value: 0.47 (silica gel; dichloromethane)

c) 1-tert.Butyloxycarbonyl-4-[4-[[4-[2-(methoxycarbonyl)-ethyl]-piperidino]-methyl]-phenyl]-piperidine

A mixture of 1.8 g (0.0058 Mol) of the compound prepared under b), 1.44 g (0.007 Mol) of methyl piperidino-propionate hydrochloride, 1.42 g (1.95 ml = 0.014 Mol) of triethylamine and 3 g of sodium iodide in 150 ml of

chloroform are refluxed for 36 hours. The undissolved components are then removed by suction filtering. The filtrate is washed twice with water, dried over sodium sulphate and evaporated to dryness in vacuo. The residue remaining is purified by chromatography over silica gel using methylene chloride/methanol (35:1) as eluant.
Yield: 2.05 g (79.8% of theory)
Resin
R_f value: 0.41 (silica gel; dichloromethane/methanol = 9.5:0.5)

The following compound was prepared analogously:

(1) 1-tert.butyloxycarbonyl-4-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminomethyl]-phenyl]-piperidine

Prepared from 1-tert.butyloxycarbonyl-4-(4-chloromethyl-phenyl)-piperidine and methyl trans-3-[4-amino-cyclohexane]-propionate
Resin

Example XVIII

1-[tert.Butyloxycarbonyl]-4-[4-[[trans-4-methoxycarbonylcyclohexyl]-aminocarbonylamino]-phenyl]-piperidine

A solution of 1.2 g (0.0044 Mol) of 1-tert.-butyloxycarbonyl-4-[4-aminophenyl]-piperidine and 0.8 g (0.0044 Mol) of trans-[4-methoxycarbonylcyclohexyl]-isocyanate in 20 ml of dioxane is heated at 50°C for 2 hours. The mixture is then evaporated to dryness under reduced pressure and the solid residue is stirred with tert.butylmethylether. The remaining solid is suction filtered, washed with tert.butylmethylether and dried.

R_f value: 0.30 (silica gel; cyclohexane/ethyl acetate = 1:1)

Example XIX

1-tert.Butyloxycarbonyl-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-piperidino]-piperidine

a) 1-tert.Butyloxycarbonyl-4-[(4-ethoxycarbonyl)-piperidino]-piperidine

A mixture of 24.9 g (0.1249 Mol) of N-tert.butyloxycarbonyl-4-piperidone, 19.3 ml (0.1249 Mol) of ethyl piperidino-4-carboxylate and 46.5 ml (0.1562 Mol) of titanium(IV)-isopropoxide is stirred for one hour at ambient temperature. Then 170 ml of anhydrous ethanol followed by 5.3 g (0.0837 Mol) of sodium cyanoborohydride are added and the mixture is stirred for a further 20 hours. Thereafter, 34 ml of water are added, the inorganic solids obtained are removed by suction filtering and washed with ethanol. The combined filtrates are evaporated to dryness. The residue remaining is dissolved in ethyl acetate. The insoluble inorganic solids are filtered off and the filtrate is evaporated to dryness in vacuo. The residue is purified by chromatography over a silica gel column using ethyl acetate/cyclohexane = 3:2 as eluant.
Yield: 32.9 g of an oily substance (77.3% of theory)
R_f value: 0.36 (silica gel; ethyl acetate)

b) 1-tert.Butyloxycarbonyl-4-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-piperidino]-piperidine

3.4 g (0.01 Mol) of the compound prepared in a) are stirred overnight in 20 ml of 1N sodium hydroxide solution. After this time, complete saponification of

the ethylester had occurred. 20 ml of 1N hydrochloric acid are added and the mixture is washed with ethyl acetate. The aqueous phase is evaporated to dryness in vacuo, the residue remaining is taken up twice in ethanol, evaporated down in vacuo and then dried at 80°C in vacuo. The residue is dissolved in 100 ml of dimethylformamide. This solution is combined with 2 ml (0.0102 Mol) of diphenyl-phosphorylchloride, cooled to -5°C, 1.4 ml (0.0102 Mol) of triethylamine are added with stirring and the mixture is stirred for a further hour at -5°C. Then 2.26 g (0.0102 Mol) of methyl trans-3-[4-aminocyclohexyl]-propionate hydrochloride and 1.4 ml (0.0102 Mol) of triethylamine are added and the mixture is stirred for a further 4 hours at ambient temperature and then for one hour at 60°C. In order to complete the reaction, another 1 ml of diphenyl-phosphorylchloride and 1.4 ml of triethylamine are added and the mixture is stirred overnight at ambient temperature. It is then evaporated to dryness in vacuo, the residue is taken up in ethyl acetate, the ethyl acetate solution is washed twice with saturated sodium hydrogen carbonate solution and once with water and dried over sodium sulphate. After evaporation in vacuo, 4 g of a residue remain which are purified by column chromatography over silica gel, using dichloromethane/methanol = 20:1 and 10:1 as eluant. The residue is triturated with ether/petroleum ether, suction filtered and dried.

Yield: 2.98 g (62.1% of theory),

Melting point: 182-184°C

Example XX

4-[4-[[trans-4-[2-(Methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-1-benzyl-piperazine

a) 1-Benzyl-4-(4-cyanophenyl)-piperazine

A mixture of 26 g (0.2147 Mol) of 4-fluorobenzonitrile, 37.3 ml (0.2147 Mol) of N-benzylpiperazine and 36.7 ml (0.2147 Mol) of N-ethyl-diisopropylamine is heated to 140°C for 8 hours. After cooling it is stirred into water and extracted with dichloromethane. The combined dichloromethane phases are dried over sodium sulphate and evaporated down in vacuo. The residue remaining is crystallised from ether/petroleum ether.
Yield: 29.8 g (50.1% of theory),
Melting point: 106-108°C

b) 1-Benzyl-4-(4-carboxyphenyl)-piperazine

29.8 g (0.1074 Mol) of 1-benzyl-4-(4-cyanophenyl)-piperazine are dissolved in 200 ml of ethyleneglycol. After the addition of 48 g (0.8592 Mol) of potassium hydroxide the mixture is refluxed for 8 hours. The ethyleneglycol is then substantially distilled off in vacuo and the remaining oil is diluted with water. After acidifying with acetic acid, the solid precipitate is suction filtered, washed with water and then with a little acetone and dried.
Yield: 31.4 g (98.7% of theory),
Melting point: 225-227°C (decomp.)

c) 4-[4-[[trans-4-[2-(Methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-1-benzyl-piperazine

To a solution of 1.5 g (0.051 Mol) of 1-benzyl-4-(4-carboxyphenyl)-piperazine in 80 ml of dimethylformamide are added, at -5°C and with stirring, 1 ml (0.0051 Mol) of diphenylphosphinic acid chloride and 0.7 ml

(0.051 Mol) of triethylamine and the mixture is stirred for a further hour at -5°C. Then 1.13 g (0.051 Mol) of methyl 3-(4-trans-aminocyclohexyl)-propionate hydrochloride and 0.7 ml (0.051 Mol) of triethylamine are added and the mixture is stirred overnight at ambient temperature. It is then evaporated to dryness in vacuo and the residue is purified by chromatography over a silica gel column, using dichloromethane which contains 2.5% methanol as eluant. The residue remaining after evaporation of the eluant is triturated with petroleum ether and suction filtered.
Yield: 1.04 g (44% of theory),
Melting point: 188-189°C

Example XXI

4-[2-[trans-4-(2-Methoxycarbonyl-ethyl)-cyclohexyl]-1-oxo-2,3-dihydro-isoindol-6-yl]-pyridine

a) Methyl 2-methyl-5-trifluoromethylsulphonyloxy-benzoate

To a solution of 10 g (60 mMol) of methyl 3-hydroxy-6-methyl-benzoate in 40 ml of dry pyridine are added dropwise, with stirring, at -8 to 4°C, 18.2 ml (66 mMol) of trifluoromethanesulphonic acid anhydride within 35 minutes. After the addition is complete the mixture is stirred overnight in an ice bath and then poured onto water. It is extracted with tert.butyl-methylether, the combined extracts are washed with dilute hydrochloric acid and then with water, dried over sodium sulphate and evaporated to dryness in vacuo. The orange-red oil remaining is purified by column chromatography over silica gel, using cyclohexane/ethyl acetate = 9:1 as eluant.
Colourless oil.
Yield: 15.3 g (85.5% of theory),

R_f value: 0.60 (silica gel; ethyl acetate/cyclohexane = 9:1)

b) Methyl 2-bromomethyl-5-trifluoromethylsulphonyloxy-benzoate

A mixture of 8.3 g (27.8 mMol) of the compound prepared under a), 5.3 g (30 mMol) of N-bromosuccinimide and 20 mg of 2,2'-azaisobutyronitrile in 100 ml of carbon tetrachloride is irradiated for one hour with a 300 W UV immersion lamp. The mixture is then cooled, the undissolved succinimide is filtered off and the filtrate is evaporated to dryness in vacuo. The residue is purified by column chromatography over silica gel using cyclohexane/ethyl acetete = 9:1 as eluant.
Colourless oil.
Yield: 7.7 g (73.3% of theory),
R_f value: 0.55 (silica gel; ethyl acetate/cyclohexane = 9:1)

c) 2-[trans-4-(2-Methoxycarbonyl-ethyl)-cyclohexyl]-1-oxo-2,3-dihydro-6-trifluoromethylsulphonyloxy-isoindole

To a solution of 2.2 g (10 mMol) of methyl trans-4-aminocyclohexylpropionate-hydrochloride and 3.9 g (5.1 ml = 30 mMol) of N,N-diisopropyl-ethylamine in 100 ml of dry dimethylformamide, a solution of 3.8 g (10 mMol) of the compound obtained in b) in 10 ml of dimethylformamide is added at ambient temperature with stirring and stirring is continued for a further 16 hours at ambient temperature. Then the mixture is evaporated down in vacuo and the residue is distributed between water and dichloromethane. The organic phase is separated off, dried over sodium sulphate and evaporated to dryness in vacuo. The solid residue is triturated with petroleum ether and suction filtered.
Yield: 1.9 g (42.2% of theory),
Melting point: 104-105°C

d) 4-[2-[trans-4-(2-Methoxycarbonyl-ethyl)-cyclohexyl]-1-oxo-2,3-dihydro-isoindol-6-yl]-pyridine

A solution of 2.3 g (5.1 mMol) of the compound obtained in c), 1 g (8 mMol) of 4-pyridyl-boric acid, 0.58 g (0.5 mMol) of tetrakis-triphenylphosphine-palladium(0) and 3.3 ml (24 mMol) of triethylamine in 35 ml of dimethylformamide is heated to 100°C for 8 hours. After cooling, the mixture is added to 150 ml of water, the precipitate is suction filtered and washed with water. After drying in vacuo at 40°C it is purified by column chromatography over silica gel, using dichloromethane/methanol = 19:1 as eluant.
Yield: 1.2 g (62.2% of theory),
Melting point: 210-211°C

Example XXII

1-Benzyl-4-[2-[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-1-oxo-2,3-dihydro-isoindol-6-yl]-3,4-dehydro-piperidine

a) 1-Benzyl-4-[2-[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-1-oxo-2,3-dihydro-isoindol-6-yl]-pyridinium-bromide

A mixture of 0.32 g (0.84 mMol) of 4-[2-[trans-4-(2-(methoxycarbonyl)-ethyl)-cyclohexyl]-1-oxo-2,3-dihydro-isoindole-pyridine, 0.2 ml (1.68 mMol) of benzylbromide and 3 ml of acetonitrile is refluxed for half an hour, during which time a solid is precipitated. After cooling and diluting with tert.butyl-methylether the mixture is suction filtered and the solid is dried at 40°C in vacuo.
Yield: 0.4 g (86.7% of theory),
Melting point: 252-255°C

b) 1-Benzyl-4-[2-[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-1-oxo-2,3-dihydro-isoindol-6-yl]-3,4-dehydro-piperidine

360 mg (0.66 mMol) of the compound obtained in a) are suspended in 10 ml of ethanol. 38 mg (1 mMol) of sodium borohydride are added in 2 batches at ambient temperature, with stirring. The mixture is stirred for a further 2 days at ambient temperature and then water is added, the mixture is extracted with ethyl acetate, the combined ethyl acetate extracts are dried over sodium sulphate and evaporated to dryness in vacuo. The crystals remaining are dried at 60°C in vacuo.
Yield: 270 mg (86.6% of theory),
Melting point: 142-143°C

Example XXIII

1-tert.butyloxycarbonyl-3-(4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-pyrrolidine

a) 4-methoxycarbonyl-trans-cinnamic acid

124.9 g (1.2 Mol) of malonic acid are dissolved in 180 ml of pyridine. 164.2 g (1 Mol) of 4-carbomethoxy-benzaldehyde and 8.52 g (0.1 Mol) of piperidine are added to this solution and the suspension thus obtained is heated to 100°C for 1½ hours. After cooling to ambient temperature the suspension is poured into 800 ml of ice/water and acidified with 200 ml concentrated hydrochloric acid. The precipitate is suction filtered, washed carefully with water, dried, triturated with acetone, further suction filtered and dried.
Yield: 185.0 g (89.72% of theory)
Melting point: 239-241°C

b) 1-Benzyl-4-[2-[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-1-oxo-2,3-dihydro-isoindol-6-yl]-3,4-dehydro-piperidine

360 mg (0.66 mMol) of the compound obtained in a) are suspended in 10 ml of ethanol. 38 mg (1 mMol) of sodium borohydride are added in 2 batches at ambient temperature, with stirring. The mixture is stirred for a further 2 days at ambient temperature and then water is added, the mixture is extracted with ethyl acetate, the combined ethyl acetate extracts are dried over sodium sulphate and evaporated to dryness in vacuo. The crystals remaining are dried at 60°C in vacuo.
Yield: 270 mg (86.6% of theory),
Melting point: 142-143°C

Example XXIII

1-tert.butyloxycarbonyl-3-(4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-pyrrolidine

a) 4-methoxycarbonyl-trans-cinnamic acid

124.9 g (1.2 Mol) of malonic acid are dissolved in 180 ml of pyridine. 164.2 g (1 Mol) of 4-carbomethoxy-benzaldehyde and 8.52 g (0.1 Mol) of piperidine are added to this solution and the suspension thus obtained is heated to 100°C for 1½ hours. After cooling to ambient temperature the suspension is poured into 800 ml of ice/water and acidified with 200 ml concentrated hydrochloric acid. The precipitate is suction filtered, washed carefully with water, dried, triturated with acetone, further suction filtered and dried.
Yield: 185.0 g (89.72% of theory)
Melting point: 329-241°C

b) methyl 4-methoxycarbonyl-trans-cinnamate

A mixture of 184.8 g (0.896 Mol) of 4-methoxycarbonyl-trans-cinnamic acid, 10 ml of sulphuric acid and 3 l of methanol is refluxed for 18 hours. After cooling with an ice bath the resulting white crystals are suction filtered, washed with methanol and dried.
Yield: 175.9 g (89.2% of theory)
Melting point: 121-123°C

c) methyl 3-(4-methoxycarbonyl-phenyl)-3-(nitro-methyl)-propionate

To a suspension of 22 g (0.1 Mol) of methyl 4-methoxycarbonyl-trans-cinnamate in 59 g (0.966 Mol) = 52 ml of nitromethane, 2.4 g (0.021 Mol) = 2.6 ml of 1,1,3,3-tetramethylguanidine are added. After heating at 70°C for 5 hours, the reaction mixture is cooled and evaporated to dryness in vacuo. The residue is divided between ethyl acetate and 2 N hydrochloric acid. The organic phase is washed with water, dried and evaporated to dryness in vacuo. The remaining crude brown oil is chromatographed over silica gel with cyclohexane/ethyl acetate (7:3 to 3:2).
Yield: 20.8 g of a light yellow oil (74% of theory)
R_f value: 0.52 (silica gel; cyclohexane/ethyl acetate = 3:2)

d) 3-(4-methoxycarbonyl-phenyl)-pyrrolidin-5-one

20.3 g (0.72 Mol) of 3-(4-methoxycarbonyl-phenyl)-3-(nitromethyl)-propionic acid are hydrogenated in 200 ml of methanol in the presence of ? g of Raney Nickel for 7 hours at 60°C under a pressure of 3 bar. The catalyst is then removed by suction filtering and the filtrate is evaporated to dryness in vacuo. The remaining crude, yellow material is triturated with dichloromethane. The resulting precipitate is suction filtered, washed with dichloromethane and dried.
Yield: 11.2 g (70.9% of theory)

Melting point: 154-156°C

e) 3-(4-methoxycarbonyl-phenyl)-pyrrolidine-hydrochloride

16.5 g (274 mMol) = 15.7 ml of glacial acetic acid are slowly added to a solution of 6 g (27 mMol) of 3-(4-methoxycarbonyl-phenyl)-pyrrolidin-5-one and 10.4 g (274 mMol) of sodium borohydride in 120 ml of dioxane with stirring and at a temperature of 10 to 15°C. The resulting mixture is refluxed for 7 hours. After stirring overnight at ambient temperature a further quantity of 5.2 g of sodium borohydride is added followed by 7.9 ml of glacial acetic acid in 30 ml of dioxane. After refluxing for a further 6 hours, the solution is evaporated to a small volume, diluted with 500 ml of water and extracted with dichloromethane. The organic phase is washed with water, dried and evaporated to a small volume. The resulting solution is treated with hydrogen chloride and evaporated to dryness.
Yield: 6.2 g of a colourless oil (93.9% of theory)
R_f value: 0.63 (Reversed Phase Plate RP8; methanol/5% sodium chloride solution = 6:4)

f) 1-tert.butyloxycarbonyl-3-(4-methoxycarbonyl-phenyl)-pyrrolidine

9.0 g (41.17 mMol) of di-tert.butyl dicarbonate are added to 6.2 g (25.6 mMol) of 3-(4-methoxycarbonyl-phenyl)-pyrrolidine-hydrochloride dissolved in a mixture of 40 ml dioxane, 20 ml water and 14.3 ml triethylamine after cooling with ice. After stirring overnight the solution is evaporated to dryness. The remaining oily substance is divided between dichloromethane and water. The organic phase is washed with water, dried and evaporated to dryness. The remaining oily substance is chromatographed over silica gel with cyclohexane/ethyl acetate (4:1).
Yield: 4.8 g of a light yellow oil (61.5% of theory)

R_f value: 0.62 (silica gel; cyclohexane/ethyl acetate = 3:2)

g) 1-tert.butyloxycarbonyl-3-(4-carboxyphenyl)-pyrrolidine

A mixture of 4.7 g (15.4 mMol) of 1-tert.butyloxycarbonyl-3-(4-methoxycarbonyl-phenyl)-pyrrolidine, 15.4 ml of 2 N sodium hydroxide, 100 ml of tetrahydrofuran and 3.3 ml of water is stirred for 24 hours at ambient temperature. A second quantity of 15.4 ml of 2 N sodium hydroxide is then added and the solution is heated to 50°C for 7 hours. After cooling to ambient temperature 31 ml of 2 N hydrochloric acid and aqueous citric acid are added to give a pH of 3. The resulting solution is evaporated to a small volume. The resulting colourless precipitate is suction filtered, washed with water and dried.
Yield: 3.8 g (84.4% of theory)
Melting point: 145-147°C

h) 1-tert.butyloxycarbonyl-3-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-pyrrolidine

A mixture of 3.75 g (12.87 mMol) of 1-tert.butyloxy-carbonyl-3-(4-carboxyphenyl)-pyrrolidine, 3.1 g (13.86 mMol) of methyl trans-(4-amino-cyclohexyl)-propionate, 7.9 g (77.67 mMol) = 10.8 ml of triethylamine and 4.45 g (13.86 mMol) of 2-[(1H)-benzotriazol-1-yl]-1,1,3,3-tetramethyluronium-tetra-fluoroborate in 100 ml of absolute dimethylformamide is stirred for 2 hours at ambient temperature. After diluting the suspension with 250 ml of water, the resulting colourless precipitate is suction filtered, washed with water and dried.
Yield: 5.75 g (100% of theory)
Melting point: 99-103°C

Example XXIV

1-tert.butyloxycarbonyl-3-[4-[[trans-4-(2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-3-methyl-pyrrolidine

a) 2-(4-methoxycarbonyl-phenyl)-pronionitrile

1.3 g of sodium hydride (55-62% in oil) are added to a solution of 5.3 g (30.25 mMol) of 4-methoxycarbonyl-phenyl-acetonitrile in 50 ml of dimethylformamide whilst cooling with ice. After ten minutes 4.3 g (30.25 mMol) = 1.9 ml of methyl iodide are added dropwise with cooling maintained. The resulting suspension is stirred for 1½ hours, diluted with water and evaporated to a small volume. The remaining solution is diluted again with water, acidified with citric acid and extracted with ethyl acetate. The combined organic phase is washed with water, dried and evaporated to dryness in vacuo. The remaining oily substance is chromatographed over silica gel with cyclohexane/ethyl acetate (17:3).
Yield: 32 g of a light yellow oil (47.1% of theory)
R_f value: 0.5 (silica, gel, cyclohexane/ethyl acetate = 7:3)

b) methyl 3-cyano-3-(4-methoxycarbonyl-phenyl)-butyrate

0.72 g of sodium hydride (55-65% in oil) are added to a solution of 3.1 g (16.38 mMol) of 2-(4-methoxycarbonyl-phenyl)-propionitrile in 50 ml of dimethylformamide whilst cooling with ice. After 15 minutes 2.5 g (16.4 mMol) = 1.55 ml of methyl bromoacetate is added dropwise whilst cooling is maintained. The resulting suspension is stirred for 2½ hours, diluted with water and evaporated to a small volume. The resulting solution is diluted again with water, acidified with citric acid and extracted with ethyl acetate. The combined organic phase is washed with water, dried and evaporated to

dryness in vacuo. The remaining oily substance is chromatographed over silica gel with cyclohexane/ethyl acetate (7:3).
Yield: 3.6 g (83.7% of theory)
Melting point: 75-77°C

c) 3-(4-methoxycarbonyl-phenyl)-3-methyl-pyrrolidin-5-one

A solution of 3.3 g (12.6 mMol) of methyl 3-cyano-3-(4-methoxycarbonyl-phenyl)-butyrate in 100 ml of methanol is acidified with 12 ml of methanolic hydrochloric acid and hydrogenated in the presence of 1 g of palladium on charcoal (10%), at a pressure of 3 bar for 6 hours at ambient temperature. After removing the catalyst by suction filtering the filtrate is evaporated to dryness in vacuo. The remaining solid is dissolved in ethyl acetate and the organic phase is extracted with water. The aqueous phase is adjusted to a pH >7 by adding a solution of potassium carbonate and then extracted with ethyl acetate. The organic phase is dried and evaporated to dryness in vacuo. The remaining solid is triturated with ethyl acetate, suction filtered, washed with ethyl acetate and dried.
Yield: 2.2 g (75.9% of theory)
Melting point: 188-189°C

d) 3-(4-methoxycarbonyl-phenyl)-3-methylpyrrolidine-hydrochloride

5.6 g (92.5 mMol) = 5.3 ml of glacial acetic acid are slowly added to a solution of 2.15 g (9.22 mMol) of 3-(4-methoxycarbonyl-phenyl)-3-methylpyrrolidine-5-one and 3.5 g (92.5 mMol) of sodium borohydride in 60 ml of dioxane with stirring and at temperature of 10 to 15°C. The mixture is refluxed for 6 hours. After stirring overnight at ambient temperature a further 1.8 g of sodium borohydride is added followed by 2.7 ml of glacial acetic acid in 10 ml of dioxane. After

refluxing for a further 7 hours the solution is evaporated to a small volume, diluted with 300 ml of water and extracted with dichloromethane. The dichloromethane phase is washed with water, dried and evaporated to a small volume. The resulting solution is treated with hydrogen chloride and evaporated to dryness.

Yield: 1.14 g of a colourless oil (48.6% of theory)

R_f value: 0.5 (Reversed Phase Plate RP8; methanol/5% sodium chloride solution = 6:7)

e) 1-tert.butyloxycarbonyl-3-(4-methoxycarbonyl-phenyl)-3-methyl-pyrrolidine

1.6 g (7.15 mMol) of di-tert.butyl dicarbonate are added to a solution of 1.14 g (4.46 mMol) of 3-(4-methoxycarbonyl-phenyl)-3-methyl-pyrrolidine-hydrochloride in a mixture of 8 ml dioxane, 4 ml water and 2.5 ml triethylamine after cooling with ice. After stirring for 2 hours the solution is evaporated to dryness and the remaining oily substance is triturated between dichloromethane and water. The organic phase is washed with water, dried and evaporated to dryness.

Yield: 1.18 g of a colourless oil (83.12% of theory)

R_f value: 0.62 (silica gel, cyclohexane/ethyl acetate = 3:2)

f) 1-tert.butyloxycarbonyl-3-(4-carboxyphenyl)-3-methyl-pyrrolidine

A mixture of 1.1 g (3.44 mMol) of 1-tert.butyloxy-carbonyl-3-(4-methoxycarbonyl-phenyl)-3-methyl-pyrrolidine, 7 ml of 2 N sodium hydroxide, 20 ml tetrahydrofuran and 1 ml water is stirred for 3 days. After this time 7 ml of 2 N hydrochloric acid and citric acid are added to give a pH of 2. The resulting solution is evaporated to a small volume and extracted with dichloromethane. The organic extract is washed with water, dried and evaporated to dryness. The

remaining oily substance is chromatographed over silica gel with cyclohexane/ethyl acetate (4:1 to 1:1).
Yield: 600 mg of a light yellow oil (51.1% of theory)
R_f value: 0.5 (silica gel; cyclohexane/ethyl acetate = 3:2)

g) 1-tert.butyloxycarbonyl-3-[4[[trans-4-(2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-1-methyl-pyrrolidine

A mixture of 0.57 g (1.87 mMol) of 1-tert.butyloxy-carbonyl-3-(4-carboxyphenyl)-3-methyl-pyrrolidine, 0.445 g (2.01 mMol) of methyl trans-(4-amino-cyclohexyl)-propionate, 1.14 g (0.113 mMol) = 1.56 ml of triethylamine and 0.645 g (2 mMol) of 2-[(1H)-benzotriazol-1-yl]-1,1,3,3-tetramethyluronium-tetrafluoroborate in 15 ml of absolute dimethylformamide is stirred for 2 hours at ambient temperature. The resulting suspension is diluted with water and evaporated to dryness. The residue is divided between ethyl acetate and a diluted potassium hydrogencarbonate solution. The organic phase is washed with water, dried and evaporated to dryness. The remaining oily substance is chromatographed over silica gel with cyclohexane/ethyl acetate = 4:1.
Yield: 300 mg of a colourless oil (37.5% of theory).
R_f value: 0.31 (silica gel; cyclohexane/ethyl acetate = 3:2)

Preparation of the end compounds:

Example 1

1-tert.Butyloxycarbonyl-4-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine

A solution of 0.76 g of 1-tert.butyloxycarbonyl-4-(4-carboxyphenyl)-piperidine, 0.90 g of 2-[(1H)-benzotriazol-1-yl]-1,1,3,3-tetramethyluronium-tetrafluoroborate, 0.55 g of methyl 3-(trans-4-amino-cyclohexyl)-propionate-hydrochloride, 0.38 g of 1-hydroxy-(1H)-benzotriazole and 0.67 g of N-methyl-morpholine in 50 ml of dimethylformamide is stirred for 16 hours at ambient temperature. The solvent is removed under reduced pressure. 200 ml of water are added to the residue and the aqueous phase is extracted with ethyl acetate. The organic phase is dried over sodium sulphate and filtered and the solvent is removed under reduced pressure. 1.8 g of a solid are obtained which is chromatographed with methylene chloride/methanol (9:1) over silica gel.
Yield: 1.15 g (98% of theory),
Melting point: sintering from 169°C
R_f value: 0.60 (silica gel; methylene chloride/methanol = 9:1)

The following compounds are obtained analogously:

(1) 1-tert.butyloxycarbonyl-4-[4-[[4-[2-(methoxycarbonyl)-ethyl]-phenyl]-aminocarbonyl]-phenyl]-piperidine
Melting point: 157-162°C
R_f value: 0.53 (silica gel; cyclohexane/ethyl acetate = 1:1)

(2) 4-[4-[[4-[2-(n-butanesulphonylamino)-2-(methoxycarbonyl)-ethyl]-phenyl]-aminocarbonyl]-phenyl]-1-tert.butyloxycarbonyl-piperidine

R_f value: 0.41 (silica gel; cyclohexane/ethyl acetate = 1:1)

Mass spectrum: $(M+Na)^+ = 624$

(3) 4-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-quinuclidine

(4) 4-[4-[[trans-4-[2-methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-pyridine

(5) 4-[4-[[4-[2-(methoxycarbonyl)-ethyl]-phenyl]-aminocarbonyl]-piperidino]-pyridine

(6) 4-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-piperidino]-pyridine

(7) 4-[4-[[4-[2-(n-butanesulphonylamino)-2-(methoxycarbonyl)-ethyl]-phenyl]-aminocarbonyl]-piperidino]-pyridine

(8) 4-[4-[[4-[2-(n-hexanoylamino)-2-(methoxycarbonyl)-ethyl]-phenyl]-aminocarbonyl]-piperidino]-pyridine

(9) 4-[4-[[trans-4-[2-(n-butanesulphonylamino)-2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-piperidino]-pyridine

(10) 4-[4-[[trans-4-[2-(n-hexanoylamino)-2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-piperidino]-pyridine

(11) 1-tert.butyloxycarbonyl-4-[4-[[trans-4-(methoxycarbonyl)-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine

Melting point: 197-200°C
R_f value: 0.20 (silica gel; methylene chloride/methanol = 20:1)

(12) 4-[4-[[4-(tert.butyloxycarbonyl-methyloxy)-phenyl]-carbonylamino]-phenyl]-1-trifluoroacetyl-piperidine
Prepared from 4-[4-amino-phenyl]-1-trifluoroacetyl-piperidine and 4-[tert.butyloxycarbonyl-methyloxy]-benzoic acid
Melting point: 177-178°C

Example 2

4-[4-[[trans-4-[2-(Methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

A mixture of 1.1 g of 1-tert.butyloxycarbonyl-4-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine, 40 ml of dioxane and 40 ml of ethereal hydrochloric acid is stirred for 5 hours at ambient temperature, during which time an oil is precipitated. The mixture of solvents is decanted off and the remaining oil is triturated with ether. The solids produced are suction filtered and dried.
Yield: 0.87 g (91% of theory),
Melting point: 225-232°C
R_f value: 0.53 (silica gel; methylene chloride/methanol/conc. ammonia = 4:1:0.25)
Mass spectrum: M^+ = 372

The following compounds are obtained analogously:

(1) 4-[4-[[4-[2-(methoxycarbonyl)-ethyl]-phenyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride
Melting point: 222-225°C
R_f value: 0.54 (silica gel; methylene chloride/methanol/conc. ammonia = 4:1:0.25)
Mass spectrum: M^+ = 366

(2) 4-[4-[[4-[2-(n-butanesulphonylamino)-2-(methoxycarbonyl)-ethyl]-phenyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride
Melting point: sintering from 70°C
R_f value: 0.63 (silica gel; methylene chloride/methanol/conc. ammonia = 4:1:0.25)
Mass spectrum: $(M+H)^+ = 502$

(3) 4-[4-[[trans-4-[2-acetamino-2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(4) 4-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-oxymethyl]-phenyl]-piperidine-hydrochloride

(5) 4-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-methyloxy]-phenyl]-piperidine-hydrochloride

(6) 4-[4-[[trans-4-[2-(n-butanesulphonylamino)-2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(7) 4-[4-[[trans-4-[2-(methanesulphonylamino)-2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(8) 4-[4-[[trans-4-[2-(n-hexanoylamino)-2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(9) 4-[4-[[trans-4-[2-(methoxycarbonyl)-propyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(10) 4-[4-[N-[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-N-methyl-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(11) 4-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-carbonylamino]-phenyl]-piperidine-hydrochloride

(12) 4-[4-[[trans-4-[3-(methoxycarbonyl)-propyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(13) 4-[4-[[trans-4-(methoxycarbonylmethyl)-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride
Melting point: >250°C
R_f value: 0.4 (Reversed Phase Plate RP8; methanol/5% sodium chloride solution = 6:4)

(14) 4-[4-[[4-[3-(methoxycarbonyl)-propyl]-piperidino]-carbonyl]-phenyl]-piperidine-hydrochloride

(15) 4-[4-[[4-[4-(methoxycarbonyl)-butyl]-piperidino]-carbonyl]-phenyl]-piperidine-hydrochloride

(16) 4-[4-[[4-[3-(methoxycarbonyl)-propyl]-piperazino]-carbonyl]-phenyl]-piperidine-dihydrochloride

(17) 4-[4-[[1-[2-(methoxycarbonyl)-ethyl]-4-piperidinyl]-aminocarbonyl]-phenyl]-piperidine-dihydrochloride

(18) 4-[4-[[4-[3-(methoxycarbonyl)-propyl]-3-oxo-piperazino]-carbonyl]-phenyl]-piperidine-hydrochloride

(19) 1-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperazine-hydrochloride
Melting point: 190-192°C

(20) 4-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-3,4-dehydro-

piperidine-hydrochloride

(21) 4-[4-[[trans-4-[2-(methoxycarbonyl)-n-octyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(22) 4-[4-[[trans-4-[2-(benzylsulphonylamino)-2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(23) 4-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-4-methyl-piperidine-hydrochloride

(24) 4-cyano-4-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(25) 4-aminocarbonyl-4-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(26) 4-(methoxycarbonyl)-4-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(27) 3-[4-[[trans-4-[2-methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-n-propylamine-hydrochloride

(28) 5-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-n-pentylamine-hydrochloride

(29) 5-[4-[[trans-4-[2-(n-butanesulphonylamino)-2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-n-pentylamine-hydrochloride

(30) 5-[4-[[trans-4-[2-(n-hexanoylamino)-2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-n-pentylamine-hydrochloride

(31) 1-[5-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-pyridin-2-yl]-piperazine-dihydrochloride

(32) 4-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-3-methyl-phenyl]-piperidine-hydrochloride

(33) 4-[3-methoxy-4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(34) 4-[4-[[trans-4-[2-amino-2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-dihydrochloride

(35) 4-[4-[[cis-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(36) 4-[4-[[cis-4-[2-(n-butanesulphonylamino)-2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(37) 4-[4-[[4-[2-(n-hexanoylamino)-2-(methoxycarbonyl)-ethyl]-phenyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(38) 4-[4-[[trans-4-(methoxycarbonylmethoxy)-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(39) 4-[3-[[4-[2-(benzylsulphonylamino)-2-

(methoxycarbonyl)-ethyl]-phenyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(40) 4-[3-[[4-[2-(n-hexanoylamino)-2-(methoxycarbonyl)-ethyl]-phenyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(41) 4-[4-[[4-[2-(benzylsulphonylamino)-2-(methoxycarbonyl)-ethyl]-phenyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(42) 4-[3-fluoro-4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(43) 4-[3-ethoxy-4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(44) 1-[2-bromo-4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperazine-hydrochloride

(45) 4-[3-chloro-4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(46) 4-[4-[[2-bromo-4-[2-(methoxycarbonyl)-ethyl]-phenyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(47) 4-[4-[[2-methoxy-4-[2-(methoxycarbonyl)-ethyl]-phenyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(48) 4-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-2-methylthio-phenyl]-piperazine-hydrochloride

(49) 1-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-2-methylsulphonyl-phenyl]-piperazine-hydrochloride

(50) 4-[4-[[4-[2-(methoxycarbonyl)-ethyl]-2-methyl-phenyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(51) 4-[4-[[4-[2-(methoxycarbonyl)-ethyl]-phenyl]-sulphonylamino]-phenyl]-piperidine-hydrochloride

(52) 4-[4-[[4-[2-(methoxycarbonyl)-ethenyl]-phenyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(53) 4-[4-[[trans-4-(methoxycarbonyl)-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride
Melting point: 260-265°C
R_f value: 0.39 (silica gel; methylene chloride/ methanol/conc. ammonia = 4:1:0.25)

(54) 4-[4-[[4-[2-(methoxycarbonyl)-ethyl]-piperidino]-methyl]-phenyl]-piperidine-dihydrochloride
Yield: 0.44 g (88 % of theory), resin;
R_f value: 0.65 (Reversed Phase Plate RP8; methanol/5% sodium chloride solution = 6:4)
^{1}H-NMR-Spectrum (200 MHz, DMSO-d_6); signals at ppm: 1.2-1.6 (m, 4H); 1.6-2.05 (m, 6+1H); 2.25-2.4 (t, 2H); 2.8-3.1 (m, 4 +1H); 3.3-3.55 (t, 4H); 3.6 (s, 3H); 4.2 (d, 2H); 7.3 (d, 2H); 7.5 (d, 2H); 8.4-8.9 (m, 2H); 9.9 (s, 1H)

(55) 1-[4-[[4-(methoxycarbonylmethoxy)-phenyl]-carbonylamino]-phenyl]-piperazine-hydrochloride

(56) 4-[4-[[4-[2-(methoxycarbonyl)-ethenyl]-phenyl]-carbonylamino]-phenyl]-piperazine-hydrochloride

(57) 4-[4-[[4-[2-(methoxycarbonyl)-ethyl]-phenyl]-

carbonylamino]-phenyl]-piperidine-hydrochloride

(58) 4-[4-[[trans-4-(methoxycarbonyl)-cyclohexyl]-methylaminocarbonyl]-phenyl]-piperidine-hydrochloride
Melting point: >250°C
R_f value: 0.43 (Reversed Phase Plate RP8; methanol/5% sodium chloride solution = 6:4)

(59) 4-[4-[[trans-4-(methoxycarbonyl)-cyclohexyl]-methylaminocarbonyl]-phenyl]-piperidine-hydrochloride
R_f value: 0.43 (Reversed Phase Plate RP8; methanol/5% sodium chloride solution = 6:4)

(60) 4-[4-[[trans-4-(methoxycarbonyl)-cyclohexyl]-aminocarbonylamino]-phenyl]-piperidine-hydrochloride

(61) 4-[4-[[trans-4-(methoxycarbonylmethoxy)-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride
R_f value: 0.6 (Reversed Phase Plate RP8; methanol/5% sodium chloride solution = 6:4)

(62) 4-[4-[[4-[2-(methoxycarbonyl)-ethyl]-piperidinyl]-carbonyl]-phenyl]-piperidine-hydrochloride
Instead of hydrochloric acid, trifluoroacetic acid was used.
Melting point: 177-179°C (decomp.)

(63) 4-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-piperidino]-piperidine-dihydrochloride
Instead of hydrochloric acid, trifluoroacetic acid was used.
Yield: 1.98 g (75.4 % of theory),
Melting point: 302-303°C (decomp.)

Example 3

4-[4-[[trans-4-(2-Carboxyethyl)-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

0.41 g of 4-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride are stirred with 80 ml of 6N hydrochloric acid for 4 hours at ambient temperature. The precipitate formed is filtered off and washed with water.

Yield: 0.33 g (84% of theory),

Melting point: 280-285°C

R_f value: 0.07 (silica gel; methylene chloride/methanol/conc. ammonia = 4:1:0.25)

Mass spectrum: $M^+ = 358$

The following compounds are obtained analogously:

(1) 4-[4-[[4-(2-carboxyethyl)-phenyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

Melting point: 290-293°C

R_f value: 0.11 (silica gel; methylene chloride/methanol/conc. ammonia = 4:1:0.25)

Mass spectrum: $M^+ = 352$

(2) 4-[4-[[4-(2-carboxyethyl)-phenyl]-aminocarbonyl]-phenyl]-1-methyl-piperidine-hydrochloride

Saponification is carried out with lithium hydroxide in a 5:4 mixture of tetrahydrofuran and water, 1N hydrochloric acid is added and the tetrahydrofuran is evaporated off in vacuo.

Melting point: above 300°C

R_f value: 0.13 (silica gel; methylene chloride/methanol/conc. ammonia = 4:1:0.25)

Mass spectrum: $M^+ = 366$

(3) 4-[4-[[4-[2-(n-butanesulphonylamino)-2-carboxy-ethyl]-phenyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride
Melting point: 130°C (sintering from 120°C)
R_f value: 0.15 (silica gel; methylene chloride/methanol/conc. ammonia = 4:1:0.25)
Mass spectrum: $(M-H)^-$ = 486

(4) 4-[3-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride
A 1:1:0.5 mixture of water, conc. hydrochloric acid and glacial acetic acid is used.
R_f value: 0.60 (Reversed Phase Plate RP8; methanol/5% sodium chloride solution = 6:4)
Mass spectrum: M^+ = 358

(5) 4-[3-[[4-(2-carboxyethyl)-phenyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride
A 1:1:1 mixture of water, conc. hydrochloric acid and glacial acetic acid is used.
R_f value: 0.43 (Reversed Phase Plate RP8; methanol/5% sodium chloride solution = 6:4)

Calc. x HCl x 1.3 H_2O:	C	60.47	H	6.67	N	6.71
Found :		60.25		6.77		6.65

(6) 4-[3-[[4-[2-(n-butanesulphonylamino)-2-carboxy-ethyl]-phenyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride
The same procedure is used as in (4).
Melting point: over 200°C
R_f value: 0.60 (Reversed Phase Plate RP8; methanol/5% sodium chloride solution = 6:4)
Mass spectrum: $(M+H)^+$ = 488

(7) 4-[4-[[trans-4-(2-acetamino-2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(8) 4-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-phenyl]-1-isopropyl-piperidine-hydrochloride

(9) 4-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-oxymethyl]-phenyl]-piperidine-hydrochloride

(10) 4-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-methyloxy]-phenyl]-piperidine-hydrochloride

(11) 4-[4-[[trans-4-[2-(n-butanesulphonylamino)-2-carboxyethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(12) 4-[4-[[trans-4-[2-carboxy-2-(methanesulphonyl-amino)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(13) 4-[4-[[trans-4-[2-carboxy-2-(n-hexanoylamino)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(14) 4-[4-[[trans-4-(2-carboxypropyl)-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(15) 4-[4-[N-[trans-4-(2-carboxyethyl)-cyclohexyl]-N-methyl-aminocarbonyl]-phenyl]-piperidine-hydrochloride
Melting point: 245-247°C

(16) 4-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-carbonylamino]-phenyl]-piperidine-hydrochloride

(17) 4-[4-[[trans-4-(3-carboxypropyl)-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(18) 4-[4-[(trans-4-carboxymethyl-cyclohexyl)-aminocarbonyl]-phenyl]-piperidine-hydrochloride

Melting point: >250°C
R_f value: 0.5 (Reversed Phase Plate RP8; methanol/5% sodium chloride solution = 6:4)

(19) 4-[4-[[4-(3-carboxypropyl)-piperidino]-carbonyl]-phenyl]-piperidine-hydrochloride

(20) 4-[4-[[4-(4-carboxybutyl)-piperidino]-carbonyl]-phenyl]-piperidine-hydrochloride

(21) 4-[4-[[4-(3-carboxypropyl)-piperazino]-carbonyl]-phenyl]-piperidine-dihydrochloride

(22) 4-[4-[[1-(2-carboxyethyl)-4-piperidinyl]-aminocarbonyl]-phenyl]-piperidine-dihydrochloride

(23) 4-[4-[[4-(3-carboxypropyl)-3-oxo-piperazino]-carbonyl]-phenyl]-piperidine-hydrochloride

(24) 1-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-phenyl]-piperazine-hydrochloride
Melting point: 300-302°C (decomp.)

(25) 4-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-phenyl]-quinuclidine-hydrochloride

(26) 4-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-phenyl]-pyridine-hydrochloride

(27) 4-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-phenyl]-3,4-dehydro-piperidine-hydrochloride

(28) 4-[4-[[trans-4-(2-carboxy-n-octyl)-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(29) 4-[4-[[trans-4-[(2-benzylsulphonylamino)-2-carboxy-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(30) 4-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-phenyl]-4-methyl-piperidine-hydrochloride

(31) 4-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-phenyl]-4-cyano-piperidine-hydrochloride

(32) 4-aminocarbonyl-4-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(33) 4-carboxy-4-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(34) 3-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-phenyl]-n-propylamine-hydrochloride

(35) 5-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-phenyl]-n-pentylamine-hydrochloride

(36) 5-[4-[[trans-4-[2-(n-butanesulphonylamino)-2-carboxyethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-n-pentylamine-hydrochloride

(37) 5-[4-[[trans-4-[2-carboxy-2-(n-hexanoylamino)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-n-pentylamine-hydrochloride

(38) 1-[5-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-pyridin-2-yl]-piperazine-dihydrochloride

(39) 4-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-3-methyl-phenyl]-piperidine-hydrochloride

(40) 4-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-3-methoxy-phenyl]-piperidine-hydrochloride
The same procedure is used as in (2)

(41) 4-[4-[[trans-4-(2-amino-2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-dihydrochloride

(42) 4-[4-[[cis-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(43) 4-[4-[[cis-4-[2-(n-butanesulphonylamino)-2-carboxy-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(44) 4-[4-[[4-[2-carboxy-2-(hexanoylamino)-ethyl]-phenyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(45) 4-[4-[[trans-4-(carboxymethoxy)-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(46) 4-[4-[[4-(2-carboxyethyl)-phenyl]-aminocarbonyl]-piperidino]-pyridine-hydrochloride

(47) 4-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-piperidino]-pyridine-hydrochloride

(48) 4-[4-[[4-[2-(n-butanesulphonylamino)-2-carboxy-ethyl]-phenyl]-aminocarbonyl]-piperidino]-pyridine-hydrochloride

(49) 4-[4-[[4-[2-carboxy-2-(n-hexanoylamino)-ethyl]-phenyl]-aminocarbonyl]-piperidino]-pyridine-hydrochloride

(50) 4-[4-[[trans-4-[2-(n-butanesulphonylamino)-2-carboxyethyl]-cyclohexyl]-aminocarbonyl]-piperidino]-pyridine-hydrochloride

(51) 4-[4-[[trans-4-[2-carboxy-2-(n-hexanoylamino)-ethyl]-cyclohexyl]-aminocarbonyl]-piperidino]-pyridine-hydrochloride

(52) 4-[3-[[4-[2-(benzylsulphonylamino)-2-carboxy-ethyl]-phenyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(53) 4-[3-[[4-[2-carboxy-2-(n-hexanoylamino)-ethyl]-phenyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(54) 4-[4-[[4-[2-(benzylsulphonylamino)-2-carboxy-ethyl]-phenyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(55) 4-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-3-fluoro-phenyl]-piperidine-hydrochloride

(56) 4-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-3-ethoxy-phenyl]-piperidine-hydrochloride
The same procedure is used as in (2)

(57) 1-[2-bromo-4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-phenyl]-piperazine-hydrochloride

(58) 4-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-3-chloro-phenyl]-piperidine-hydrochloride

(59) 4-[4-[[2-bromo-4-(2-carboxyethyl)-phenyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(60) 4-[4-[[4-(2-carboxyethyl)-2-methoxy-phenyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(61) 1-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-2-methylthio-phenyl]-piperazine-hydrochloride

(62) 1-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-2-methylsulphonyl-phenyl]-piperazine-hydrochloride

(63) 4-[4-[[4-(2-carboxyethyl)-2-methyl-phenyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(64) 4-[4-[[4-(2-carboxyethyl)-phenyl]-sulphonylamino]-phenyl]-piperidine-hydrochloride

(65) 4-[4-[[4-(2-carboxyethenyl)-phenyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(66) 4-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-phenyl]-1-methyl-piperidine-hydrochloride
Melting point: >300°C
Mass spectrum: $M^+ = 372$

(67) 4-[1-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-piperidino]-piperidine-hydrochloride

(68) 4-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-piperidino]-piperidine-dihydrochloride
Yield: 0.77 g (79.5% of theory),
Melting point: 297-300°C (decomp.)

(69) 1-[4-[[4-(carboxymethoxy)-phenyl]-carbonylamino]-phenyl]-piperazine-hydrochloride

(70) 4-[4-[[4-(2-carboxyethenyl)-phenyl]-carbonylamino]-phenyl]-piperidine-hydrochloride

(71) 4-[4-[[4-(2-carboxyethyl)-phenyl]-carbonylamino]-phenyl]-piperidine-hydrochloride

(72) 4-[4-[[trans-4-(carbcxy)-cyclohexyl]-methyl-aminocarbonyl]-phenyl]-piperidine-hydrochloride
Melting point: 109-110°C

(73) 4-[2-[4-(2-carboxyethyl)-phenyl]-1-oxo-2,3-dihydro-isoindol-6-yl]-piperidine-hydrochloride
Melting point: 291-293°C
R_f value: 0.52 (Reversed Phase Plate RP8; methanol/5% sodium chloride solution = 6:4)

(74) 2-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-phenyl]-ethylamine-hydrochloride
Melting point: >250°C
R_f value: 0.65 (Reversed Phase Plate RP8; methanol/5% sodium chloride solution = 6:4)

(75) 4-[4-[[trans-4-(carboxymethoxy)-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride
Melting point: >250°C
R_f value: 0.65 (Reversed Phase Plate RP8; methanol/5% sodium chloride solution = 6:4)

(76) 4-[4-[[trans-4-carboxy-cyclohexyl]-aminocarbonyamino]-phenyl]-piperidine-hydrochloride
Melting point: >200°C
R_f value: 0.70 (Reversed Phase Plate RP8; methanol/5% sodium chloride solution = 6:4)

(77) 4-[4-[[4-(2-carboxyethyl)-phenyl]-aminomethyl]-phenyl]-piperidine-hydrochloride

(78) 4-[4-[[4-(2-carboxyethyl)-piperidinyl]-carbonyl]-phenyl]-piperidine-hydrochloride
Melting point: 207-208°C (decomp.)

(79) 4-[2-[trans-4-(2-carboxyethyl)-cyclohexyl]-1-oxo-2,3-dihydro-isoindol-6-yl]-piperidine-hydrochloride
R_f value: 0.50 (Reversed Phase Plate RP8; methanol/5% sodium chloride solution = 6:4)

(80) 4-[2-[trans-4-(2-carboxyethyl)-cyclohexyl]-1-oxo-2,3-dihydro-isoindol-5-yl]-piperidine-hydrochloride
R_f value: 0.50 (Reversed Phase Plate RP8; methanol/5% sodium chloride solution = 6:4)
Melting point: >300°C

(81) 4-[2-[4-(2-carboxyethyl)-phenyl]-1-oxo-2,3-dihydro-isoindol-5-yl]-piperidine-hydrochloride
Melting point: 303-306°C

(82) 4-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-phenyl]-1-aza-bicyclo[2.2.1]heptane-hydrochloride

(83) 4-[4-[[trans-4-(carboxy)-cyclohexyl]-methylaminocarbonyl]-piperidine-hydrochloride
R_f value: 0.56 (Reversed Phase Plate RP8; methanol/5% sodium chloride solution = 6:4)

Example 4

4-[4-[[4-[2-(Methoxycarbonyl)-ethyl]-phenyl]-aminocarbonyl]-phenyl]-1-methyl-piperidine-hydrochloride

0.8 g of 4-[4-[[4-[2-(methoxycarbonyl)-ethyl]-phenyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride are dissolved in 35 ml of methanol, mixed with 0.42 g of paraformaldehyde and 0.45 g of sodium cyanoborohydride

and stirred for 3 hours at ambient temperature, whilst the pH is maintained between 3 and 6 by the addition of 1N hydrochloric acid. Then a further 0.5 g of paraformaldehyde and 0.5 g of sodium cyanoborohydride are added and the mixture is stirred for 16 hours at ambient temperature whilst maintaining the above-mentioned acidity of the solution. It is then made alkaline with 10N sodium hydroxide solution, extracted with ethyl acetate, the organic phase is evaporated down and purified by chromatography on silica gel (eluant: methylene chloride/methanol = 9:1).
Yield: 0.58 g (76% of theory),
Melting point: 161-164°C
R_f value: 0.17 (silica gel; methylene chloride/methanol = 9:1)
Mass spectrum: $M^+ = 380$

The following compounds are obtained analogously:

(1) 1-isopropyl-4-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine

(2) 4-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-1-methyl-piperidine
Melting point: 202-204°C

(3) 4-[2-[trans-4-(2-carboxy-ethyl)cyclohexyl]-1-oxo-2,3-dihydro-isoindol-5-yl]-1-methyl-piperidine-hydrochloride
Melting point: 301-303°C
Prepared from 4-[2-(trans-4-(2-carboxy-ethyl)-cyclohexyl]-1-oxo-2,3-dihydro-isoindol-5-yl]-piperidine with paraformaldehyde and formic acid.

(4) 3-[4-[[trans-4-(2-carboxyethyl)cyclohexyl]-aminocarbonyl]-phenyl]-1-methyl-pyrrolidine-hydrochloride

Melting point: 246-250°C
Prepared from 3-[4-[[trans-4-(2-carboxy-ethyl)-cyclohexyl]-aminocarbonyl]-phenyl]-pyrrolidine-hydrochloride with paraformaldehyde and formic acid.

Example 5

4-[3-[[trans-4-[2-(Methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

---

1.7 g of 1-benzyl-4-[3-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-3,4-dehydro-piperidine are dissolved in 40 ml of methanol, mixed with 2 ml of methanolic hydrochloric acid and 0.5 g of palladium hydroxide on charcoal and hydrogenated with hydrogen under 5 bars of pressure at 50°C. Then the catalyst is filtered off and the filtrate is evaporated down in vacuo.
Yield: 1.30 g (87% of theory),
R_f value: 0.25 (Reversed Phase Plate RP8; methanol/5% sodium chloride solution = 6:4)
Mass spectrum: $M^+ = 372$

The following compounds are obtained analogously:

(1) 4-[3-[[4-[2-(methoxycarbonyl)-ethyl]-phenyl]-aminocarbonyl]-phenyl]-piperidine
The work is done without the addition of hydrochloric acid, using 10% palladium charcoal.
R_f value: 0.27 (Reversed Phase Plate RP8; methanol/5% sodium chloride solution = 6:4)

(2) 4-[3-[[4-[2-(n-butanesulphonylamino)-2-(methoxycarbonyl)-ethyl]-phenyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride
The same procedure is used as in (1) but at 60°C.
R_f value: 0.28 (Reversed Phase Plate RP8; methanol/5%

sodium chloride solution = 6:4)
Mass spectrum: $(M+H)^+$ = 502

(3) 1-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperazine-hydrochloride
Prepared by debenzylation of 4-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-1-benzyl-piperazine in the presence of 10% palladium charcoal.
Melting point: 190-192°C

(4) 4-[2-[4-[2-(methoxycarbonyl)-ethyl]-phenyl]-1-oxo-2,3-dihydro-isoindol-6-yl]-piperidine-hydrochloride

(5) 4-[2-[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-1-oxo-2,3-dihydro-isoindol-6-yl]-piperidine-hydrochloride
Melting point: 175-178°C
Prepared from 1-benzyl-4-[2-[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-1-oxo-2,3-dihydro-isoindol-6-yl]-3,4-dehydro-piperidine and palladium hydroxide on charcoal as catalyst.

(6) 4-[2-[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-1-oxo-2,3-dihydro-isoindol-5-yl]-piperidine-hydrochloride
Melting point: 260-262°C

(7) 4-[2-[4-[2-(methoxycarbonyl)-ethyl]-phenyl]-1-oxo-2,3-dihydro-isoindol-5-yl]-piperidine-hydrochloride
Melting point: 232-235°C

Example 6

1-Benzyl-4-[3-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-3,4-dehydro-piperidine

---

2 g of 1-Benzyl-4-(3-carboxyphenyl)-3,4-dehydro-piperidine-hydrochloride are refluxed for 45 minutes in 3.5 ml of thionylchloride and then evaporated to dryness in vacuo. The acid chloride thus obtained is added in batches to a solution (cooled to 0°C) of 1.3 g of methyl 3-(trans-4-amino-cyclohexyl)-propionate-hydrochloride and 3.3 ml of N-ethyl-diisopropylamine in 50 ml of methylene chloride. After 2 hours, 300 ml of methylene chloride and 15 ml of methanol are added, the mixture is washed successively with water, 0.1N sodium hydroxide solution, water, 0.1N hydrochloric acid and water and the organic phase is evaporated down. The product is purified by column chromatography over silica gel (eluant: methylene chloride/methanol = 9:1)
Yield: 1.8 g (64% of theory),
R_f value: 0.42 (silica gel; methylene chloride/methanol = 9:1)

The following compounds are obtained analogously:

(1) 1-benzyl-4-[3-[[4-[2-(methoxycarbonyl)-ethyl]-phenyl]-aminocarbonyl]-phenyl]-3,4-dehydro-piperidine
Melting point: 194-196°C
R_f value: 0.66 (silica gel; methylene chloride/methanol = 9:1)

(2) 1-benzyl-4-[3-[[4-[2-(n-butanesulphonylamino)-2-(methoxycarbonyl)-ethyl]-phenyl]-aminocarbonyl]-phenyl]-3,4-dehydro-piperidine-hydrochloride
R_f value: 0.25 (silica gel; methylene chloride/methanol = 20:1)

Example 7

4-[4-[[4-(2-Carboxyethyl)-phenyl]-aminomethyl]-phenyl]-piperidine-hydrochloride

---

0.7 g of 4-[4-[[4-[2-(methoxycarbonyl)-ethyl]-phenyl]-aminomethyl]-phenyl]-1-trifluoroacetyl-piperidine, 10 ml of glacial acetic acid and 1 ml of conc. hydrochloric acid are stirred for 4 hours at 80°C and for 16 hours at ambient temperature. The mixture is evaporated to dryness in vacuo, evaporated down several times with toluene and the residue is stirred with 50 ml of acetone.

Yield: 0.39 g (66% of theory),

R_f value: 0.76 (Reversed Phase Plate RP8; methanol/5% sodium chloride solution = 9:1)

Mass spectrum: $M^+ = 338$

The following compounds are obtained analogously:

(1) 4-[2-[trans-4-(2-carboxyethyl)-cyclohexyl]-1-oxo-2,3-dihydro-isoindol-6-yl]-piperidine-hydrochloride

(2) 4-[2-[4-[2-(n-butanesulphonylamino)-2-carboxy-ethyl]-phenyl]-1-oxo-2,3-dihydro-isoindol-6-yl]-piperidine-hydrochloride

(3) 4-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminomethyl]-phenyl]-piperidine-dihydrochloride
Melting point: 308-311°C (decomp.)

(4) 4-[4-[N-[trans-4-(2-carboxyethyl)-cyclohexyl]-N-methylaminomethyl]-phenyl]-piperidine-dihydrochloride

(5) 4-[4-[N-[trans-4-(2-carboxyethyl)-cyclohexyl]-N-(2-phenyl-ethyl)-aminomethyl]-phenyl]-piperidine-dihydrochloride

(6) 4-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminosulphonyl]-phenyl]-piperidine-hydrochloride

(7) 4-[4-[2-[4-(2-carboxyethyl)-phenyl]-ethenyl]-phenyl]-piperidine-hydrochloride

(8) 4-[2-[trans-4-(2-carboxyethyl)-cyclohexyl]-1-oxo-2,3-dihydro-isoindol-5-yl]-piperidine-hydrochloride

(9) 4-[2-[4-(2-carboxyethyl)-phenyl]-1-oxo-2,3-dihydro-isoindol-5-yl]-piperidine-hydrochloride

(10) 4-[2-[4-[2-(n-butanesulphonylamino)-2-carboxy-ethyl]-phenyl]-1-oxo-2,3-dihydro-isoindol-5-yl]-piperidine-hydrochloride

(11) 4-[2-[trans-4-(2-carboxyethyl)-cyclohexyl]-1-oxo-3,4-dihydro-isoquinolin-7-yl]-piperidine-hydrochloride

(12) 4-[2-[4-(2-carboxyethyl)-phenyl]-1-oxo-3,4-dihydro-isoquinolin-7-yl]-piperidine-hydrochloride

(13) 4-[2-[4-(2-carboxyethyl)-phenyl]-1-oxo-2,3-dihydro-isoindol-6-yl]-piperidine-hydrochloride

(14) 4-[4-[2-[4-(2-carboxyethyl)-phenyl]-ethyl]-phenyl]-piperidine-hydrochloride

(15) 4-[4-[[4-(2-carboxyethyl)-phenyl]-methylamino]-phenyl]-piperidine-hydrochloride

(16) 4-[4-[(trans-4-carboxy-cyclohexyl)-aminocarbonyl]-phenyl]-piperidine-hydrochloride
Melting point: above 310°C
R_f value: 0.13 (silica gel; methylene chloride/methanol/conc. ammonia = 4:1:0.25)

(17) 4-[4-[[4-(carboxymethyloxy)-phenyl]-carbonylamino]-phenyl]-piperidine-hydrochloride

Prepared from 4-[4-[[4-(tert.bucyloxycarbonyl-methyloxy)-phenyl]-carbonylamino]-phenyl]-1-trifluoroacetyl-piperidine

R_f value: 0.10 (silica gel; methylene chloride/methanol = 9:1)

Mass spectrum: $(M+H)^+ = 355$

Example 8

4-[4-[[4-[2-(Methoxycarbonyl)-ethyl]-phenyl]-aminomethyl]-phenyl]-1-trifluoroacetyl-piperidine

---

8.6 g of 4-[4-[[4-[2-(methoxycarbonyl)-ethyl]-phenyl]-iminomethyl]-phenyl]-1-trifluoroacetyl-piperidine are dissolved in 100 ml of ethyl acetate and hydrogenated initially for 1.5 hours in the presence of 0.5 g of platinum dioxide at ambient temperature using a hydrogen pressure of 5 bar. A further 0.5 g of platinum dioxide are added and the temperature is increased to 50°C. After 3 hours a further 0.5 g of platinum dioxide are added and hydrogenation is continued for a further 4 hours. After the catalyst has been filtered off the solvent is removed and the residue is purified by column chromatography over silica gel (eluant: cyclohexane/ethyl acetate = 3:1)

Yield: 3.6 g (42% of theory),

R_f value: 0.50 (silica gel; cyclohexane/ethyl acetate = 2:1)

Example 9

4-[4-[[trans-4-[2-(Isopropyloxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

0.15 g of 4-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride are suspended in a mixture of 100 ml of isopropanol and 50 ml of ethereal hydrochloric acid and stirred for 16 hours at ambient temperature. The product is obtained by evaporating the solution down in vacuo.
Yield: 0.135 g (81% of theory),
Melting point: 255-260°C
R_f value: 0.31 (silica gel; methylene chloride/methanol/conc. ammonia = 4:1:0.25)
Mass spectrum: $M^+ = 400$

The following compounds are obtained analogously:

(1) 4-[4-[[trans-4-[2-(sec.butyloxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(2) 4-[4-[[trans-4-[2-(cyclohexyloxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride
Melting point: 238-240°C

(3) 4-[4-[[trans-4-[2-(isobutyloxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride
Melting point: 238-240°C

(4) 4-[4-[[trans-4-[2-[(2-phenylethyl)-oxycarbonyl]-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride

(5) 4-[2-[4-[2-(methoxycarbonyl)-ethyl]-phenyl]-1-oxo-2,3-dihydro-isoindol-6-yl]-piperidine-hydrochloride

(6) 4-[2-[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-1-oxo-2,3-dihydro-isoindol-6-yl]-piperidine-hydrochloride

(7) 4-[2-[4-[2-(n-butanesulphonylamino)-2-(methoxycarbonyl)-ethyl]-phenyl]-1-oxo-2,3-dihydro-isoindol-6-yl]-piperidine-hydrochloride

(8) 4-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminomethyl]-phenyl]-piperidine-di-trifluoroacetate
Melting point: 77-79°C (decomp.)

(9) 4-[4-[N-[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-N-methyl-aminomethyl]-phenyl]-piperidine-dihydrochloride

(10) 4-[4-[N-[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-N-(2-phenylethyl)-aminomethyl]-phenyl]-piperidine-dihydrochloride

(11) 4-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminosulphonyl]-phenyl]-piperidine-hydrochloride

(12) 4-[4-[2-[4-[2-(methoxycarbonyl)-ethyl]-phenyl]-ethenyl]-phenyl]-piperidine-hydrochloride

(13) 4-[2-[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-1-oxo-2,3-dihydro-isoindol-5-yl]-piperidine-hydrochloride

(14) 4-[2-[4-[2-(methoxycarbonyl)-ethyl]-phenyl]-1-oxo-2,3-dihydro-isoindol-5-yl]-piperidine-hydrochloride

(15) 4-[2-[4-[2-(n-butanesulphonylamino)-2-(methoxycarbonyl)-ethyl]-phenyl]-1-oxo-2,3-dihydro-isoindol-5-yl]-piperidine-hydrochloride

(16) 4-[2-[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-1-oxo-3,4-dihydro-isoquinolin-7-yl]-piperidine-hydrochloride

(17) 4-[2-[4-[2-(methoxycarbonyl)-ethyl]-phenyl]-1-oxo-3,4-dihydro-isoquinolin-7-yl]-piperidine-hydrochloride

(18) 4-[4-[2-[4-[2-(methoxycarbonyl)-ethyl]-phenyl]-ethyl]-phenyl]-piperidine-hydrochloride

(19) 4-[4-[[4-[2-(methoxycarbonyl)-ethyl]-phenyl]-methylamino]-phenyl]-piperidine-hydrochloride

(20) 4-[4-[[4-[2-(methoxycarbonyl)-ethyl]-phenyl]-aminomethyl]-phenyl]-piperidine-hydrochloride

(21) 4-[4-[[trans-4-(isopropylcarbonyl)-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride
Melting point: 270°C (sintering from 250°C)
R_f value: 0.38 (silica gel; methylene chloride/methanol/conc. ammonia = 4:1:0.25)

(22) 4-[4-[[trans-4-[2-(ethoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride
Melting point: 246-248°C

(23) 4-[4-[[trans-4-(ethoxycarbonyl-methyloxy)-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine-hydrochloride
R_f value: 0.60 (Reversed Phase Plate RP8; methanol/5% sodium chloride solution = 6:4)

(24) 4-[4-[[4-(methoxycarbonyl-methyloxy)-phenyl]-carbonylamino]-phenyl]-piperidine

(25) 4-[2-[trans-4-[2-(ethoxycarbonyl)-ethyl]-cyclohexyl]-1-oxo-2,3-dihydro-isoindol-5-yl]-piperidine-hydrochloride
Melting point: 260-264°C

Example 10

1-(Methoxycarbonyl)-4-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine

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Prepared from 4-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine and methylchloroformate in methylene chloride in the presence of 0.2N sodium hydroxide solution.

The following compound is obtained analogously:

(1) 1-(acetoxy-methoxycarbonyl)-4-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine

Example 11

2-[4-[[trans-4-[2-(Methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-ethylamine-hydrochloride

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A solution of 1.6 g (4.87 mMol) of 2-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-acetonitrile in 400 ml of methanol is acidified with methanolic hydrochloric acid and then hydrogenated in the presence of 0.5 g of palladium on charcoal (10%) at ambient temperature under a pressure of 3 bar until the uptake of hydrogen has ceased. Then the catalyst is

removed by suction filtering and the filtrate is evaporated to dryness under reduced pressure. The residue is triturated with a 1:1 mixture of tert.butyl-methylether and ethyl acetate, heated, cooled down to ambient temperature once more and suction filtered. After decoction with acetone and suction filtering again, 1.2 g = 66.7% of a yellowish crystalline compound are obtained.

Melting point: >250°C

R_f value: 0.45 (silica gel; dichloromethane/methanol = 4:1)

Example 12

4-[1-[[trans-4-[2-(Methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-piperidino]-piperidine

To an equimolar solution of trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexylamine and p-nitrophenyl chloroformate in dry tetrahydrofuran, a solution of 2 equivalents of triethylamine in tetrahydrofuran is added dropwise with stirring at 0°C and the resulting mixture is stirred for another 2.5 hours at 0°C. Then, as stirring continues, one equivalent of 4,4'-bipiperidyl is added dropwise, the mixture is then stirred for 16 hours at ambient temperature and for another 4 hours at 50°C. Then it is evaporated to dryness under reduced pressure, the residue is taken up in ethyl acetate and this ethyl acetate solution is washed with 1N sodium hydroxide solution and then with water, dried over sodium sulphate and evaporated to dryness under reduced pressure. The crude product remaining is chromatographed over silica gel, using ethyl acetate as eluant.

removed by suction filtering and the filtrate is evaporated to dryness under reduced pressure. The residue is triturated with a 1:1 mixture of tert.butyl-methylether and ethyl acetate, heated, cooled down to ambient temperature once more and suction filtered. After decoction with acetone and suction filtering again, 1.2 g = 66.7% of a yellowish crystalline compound are obtained.

Melting point: >250°C

R_f value: 0.45 (silica gel; dichloromethane/methanol = 4:1)

Example 12

4-[1-[[trans-4-[2-(Methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-piperidino]-piperidine

To an equimolar solution of trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexylamine and p-nitrophenyl chloroformate in dry tetrahydrofuran, a solution of 2 equivalents of triethylamine in tetrahydrofuran is added dropwise with stirring at 0°C and the resulting mixture is stirred for another 2.5 hours at 0°C. Then, as stirring continues, one equivalent of 4,4'-bipiperidyl is added dropwise, the mixture is then stirred for 16 hours at ambient temperature and for another 4 hours at 50°C. Then it is evaporated to dryness under reduced pressure, the residue is taken up in ethyl acetate and this ethyl acetate solution is washed with 1N sodium hydroxide solution and then with water, dried over sodium sulphate and evaporated to dryness under reduced pressure. The crude product remaining is chromatographed over silica gel, using ethyl acetate as eluant.

Example 13

4-[4-[[4-(2-Carboxyethyl)-piperidino]-methyl]-phenyl]-piperidine-dihydrochloride

1.3 g (0.0029 Mol) of 1-tert.butyloxycarbonyl-4-[4-[[2-(methoxycarbonylethyl)-piperidino]-methyl]-phenyl]-piperidine are stirred for 15 minutes at ambient temperature in 80 ml of semiconcentrated hydrochloric acid. Then the mixture is evaporated to dryness in vacuo and the residue remaining is digested three times with acetone and the resinous residue remaining is dried in vacuo.

Yield: 0.82 g (77.1% of theory),

R_f value: 0.54 (Reversed Phase Plate RP8; methanol/5% sodium chloride solution = 6:4)

^{1}H-NMR spectrum (200 MHz, DMSO-d_6); signals at p[illegible] 1.3-1.7 (m, 5H), 1.7-2.0 (m, 6H); 2.15-2.3 (t, 2H); [illegible] 3.1 (m, 4+1H); 3.2-3.55 (m, 4H); 4.15-4.2 (d, 2H); [illegible] (d, 2H); 7.6 (d, 2H); 9.1 (s, 2H); 10.7 (s, 1H); 12.05 (s, 1H)

The following compounds are prepared analogously:

(1) 4-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminomethyl]-phenyl]-piperidine-dihydrochloride
Melting point: 308-311°C (decomp.)
Prepared from 1-tert.butyloxycarbonyl-4-[4-[[trans-4-(2-methoxycarbonyl-ethyl)-cyclohexyl]-aminomethyl]-phenyl]-piperidine and semiconcentrated hydrochloric acid.

(2) 3-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-phenyl]-pyrrolidine-hydrochloride

(3) 3-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-phenyl]-3-methyl-pyrrolidine-hydrochloride

(4) 4-[2-[trans-4-(2-carboxyethyl)-cyclohexyl]-1-oxo-2,3-dihydro-isoindol-6-yl]-pyridine
R_f value: 0.39 (Reversed Phase Plate RP8; methanol/5% sodium chloride solution = 6:4)

(5) 1-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminomethyl]-phenyl]-piperazine-dihydrochloride
Melting point: 245-248°C (decomp.)
Prepared from 1-tert.butyloxycarbonyl-4-[4-[[trans-4-(2-methoxycarbonyl-ethyl)-cyclohexyl]-aminomethyl]-phenyl]-piperazine and semiconcentrated hydrochloric acid.

(6) 3-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-amino-carbonyl]-phenyl]-pyrrolidine-hydrochloride
Melting point: > 250°C
R_f value: 0.55 (Reversed Phase Plate RP8; methanol/5% sodium chloride solution = 6/4)
Prepared from 1-tert.butyloxycarboxyl-3-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-pyrrolidine and half-concentrated hydrochloric acid.

(7) 3-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-amino-carbonyl]-phenyl]-3-methyl-pyrrolidine-hydrochloride
Melting point: >250°C
R_f value: 0.5 (Reversed Phase Plate RP8; methanol/5% sodium chloride solution = 6/4)
Prepared from 1-tert.butyloxycarbonyl-3-[4-[[trans-4-[2-(methoxycarbonylethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-3-methyl-pyrrolidine and semi-concentrated hydrochloric acid.

Example 14

Dry ampoule containing 2.5 mg of active substance per 1 ml

Composition:

Active substance	2.5 mg
Mannitol	50.0 mg
Water for injections ad	1.0 ml

Preparation:

The active substance and mannitol are dissolved in water. After transferring the solution to the ampoule, it is freeze-dried.

When required for use, the solution is made up with water for injections.

Example 15

Dry ampoule containing 35 mg of active substance per 2 ml

Composition:

Active substance	35.0 mg
Mannitol	100.0 mg
Water for injections ad	2.0 ml

Preparation:

The active substance and mannitol are dissolved in water. After transferring the solution to the ampoule,

it is freeze-dried.

When required for use, the solution is made up with water for injections.

Example 16

Tablet containing 50 mg of active substance

Composition:

(1) Active substance	50.0 mg
(2) Lactose	98.0 mg
(3) Corn starch	50.0 mg
(4) Polyvinylpyrrolidone	15.0 mg
(5) Magnesium stearate	2.0 mg
	215.0 mg

Preparation:

Components (1), (2) and (3) are mixed together and granulated with an aqueous solution of component (4). Component (5) is added to the dried granules. From this mixture, compressed tablets are produced, biplanar, facetted on both sides and notched on one side. Diameter of tablets: 9 mm.

Example 17

Tablet containing 350 mg of active substance

Composition:

(1) Active substance	350.0 mg
(2) Lactose	136.0 mg
(3) Corn starch	80.0 mg
(4) Polyvinylpyrrolidone	30.0 mg
(5) Magnesium stearate	4.0 mg
	600.0 mg

Preparation:

Components (1), (2) and (3) are mixed together and granulated with an aqueous solution of component (4). Component (5) is added to the dried granules. From this mixture, compressed tablets are produced, biplanar, facetted on both sides and notched on one side. Diameter of tablets: 12 mm.

Example 18

Capsules containing 50 mg of active substance

Composition:

(1) Active substance	50.0 mg
(2) Dried corn starch	58.0 mg
(3) Powdered lactose	50.0 mg
(4) Magnesium stearate	2.0 mg
	160.0 mg

Preparation:

Component (1) is triturated with component (3). This triturate is added to the mixture of components (2) and (4), with thorough mixing.

This powdered mixture is packed into size 3 hard gelatin oblong capsules in a capsule filling machine.

Example 19

Capsules containing 350 mg of active substance

Composition:

(1) Active substance	350.0 mg
(2) Dried corn starch	46.0 mg
(3) Powdered lactose	30.0 mg
(4) Magnesium stearate	4.0 mg
	430.0 mg

Preparation:

Component (1) is triturated with component (3). This triturate is added to the mixture of components (2) and (4), with thorough mixing.

This powdered mixture is packed into size 0 hard gelatin oblong capsules in a capsule filling machine.

[redacted] The claims defining the invention are as follows:-

1. Compounds of formula I

$$A - B - C - D - E - COOR_a \qquad (I)$$

(wherein:

R_a denotes a hydrogen atom or a C_{1-5}-alkyl, C_{3-5}-alkenyl, phenyl(C_{1-3}-alkyl), C_{5-7}-cycloalkyl or R_1-CO-O-(R_2CH)- group;

R_1 denotes a C_{1-5}-alkyl, C_{5-7}-cycloalkyl, phenyl(C_{1-3}-alkyl), C_{1-5}-alkoxy, C_{5-7}-cycloalkoxy or phenyl group;

R_2 denotes a hydrogen atom or a C_{1-4}-alkyl, C_{5-7}-cycloalkyl or phenyl group;

A denotes a C_{1-5}-aminoalkyl group linked to group B via a carbon atom of A, or A denotes a 5-, 6- or 7-membered azacycloalkyl group linked to group B via a carbon atom of the azacycloalkyl group, or A denotes a quinuclidinyl or pyridyl group, wherein the nitrogen in the above-mentioned aminoalkyl or azacycloalkyl groups is optionally substituted by a group R_b, wherein the carbon atoms of the azacycloalkyl group are optionally substituted by 1 to 3 C_{1-3}-alkyl groups or by an aminocarbonyl, cyano, R_3O- or R_3O-CO- group,

wherein, in a 6- or 7-membered azacycloalkyl group A a >CH- unit in the 4-position relative to the ring nitrogen is optionally replaced by a nitrogen atom, wherein in a 5-, 6- or 7-membered azacycloalkyl group A a $-CH_2-CH<$ unit may be replaced by a -CH=C< unit and wherein in a piperazinyl or homopiperazinyl group A a ring carbon adjacent to the nitrogen atom in the 4-position is optionally oxo-substituted;

R_6 denotes a C_{1-3}-alkyl, phenyl(C_{1-3}-alkyl), C_{2-4}-alkanoyl, trifluoroacetyl, (C_{1-5}-alkoxy)carbonyl, phenyl(C_{1-3}-alkoxy)carbonyl, (C_{3-5}-alkenyl)oxycarbonyl or an R_1-CO-O-(R_2CH)-O-CO- group;

R_3 denotes a hydrogen atom, or a C_{1-3}-alkyl or phenyl-(C_{1-3})-alkyl group,

B denotes a phenylene group optionally mono- or disubstituted by fluorine, chlorine or bromine atoms, by trifluoromethyl groups, or by C_{1-3}-alkyl, C_{1-3}-alkoxy, C_{1-3}-alkylsulphenyl, C_{1-3}-alkylsulphinyl or C_{1-3}-alkylsulphonyl groups, wherein the substituents may be identical or different and wherein, additionally, 1 or 2 unsubstituted methine groups may each be replaced by an N-atom, or B denotes a piperidinylene group,

C denotes a carbonyl, $-CH_2CH_2-$, -CH=CH-, $-CH_2-$, $-CH_2O-$, $-OCH_2-$, $-CONR_4-$, $-CONR_4-CH_2-$, $-NR_4CO-$, $-NR_4CO-NR_4-$, $-CH_2NR_4-$, $-NR_4CH_2-$, $-SO_2NR_4-$, $-SO_2NR_4-CH_2-$ or $-NR_4SO_2-$ group;

R_4 denotes a hydrogen atom or a C_{1-3}-alkyl or phenyl(C_{1-3}-alkyl) group, or if C denotes a $-CONR_4-$ group bound to group B via the carbonyl group, R_4 may also denote a methylene or 1,2-ethylene group bound to the carbon atom of group B in the ortho-position relative to the point of linkage of the $-CONR_4-$ group;

D denotes a phenylene group optionally mono- or disubstituted by fluorine, chlorine or bromine atoms, by trifluoromethyl groups, by C_{1-3}-alkyl, C_{1-3}-alkoxy, C_{1-3}-alkylsulphenyl, C_{1-3}-alkylsulphinyl or C_{1-3}-alkylsulphonyl groups, wherein the substituents may be identical or different, and wherein additionally 1 or 2 unsubstituted methine groups may each be replaced by an N-atom, or D denotes a C_{5-7}-cycloalkylene group wherein one or two >CH- units may be replaced by an N-atom and additionally

in an aza- or diazacyclohexylene ring thus formed, a ring carbon adjacent to a ring nitrogen is optionally oxo-substituted;

E denotes a bond, a C_{1-3}-alkyleneoxy group bound to group D through the oxygen atom, a straight-chain C_{1-5}-alkylene group optionally substituted by 1 or 2 C_{1-8}-alkyl groups, or by a hydroxy, C_{1-8}-alkoxy, R_5NH-, $R_5N(C_{1-8}alkyl)$ or $R_5N(phenylC_{1-3}$-alkyl) group, or E denotes a C_{2-5}-alkenylene group optionally substituted by one or two C_{1-8}-alkyl groups;

R_5 denotes a hydrogen atom or a C_{1-8}-alkyl, (C_{1-4}-alkoxy)carbonyl, or phenyl(C_{1-3}-alkoxy)carbonyl group or a carbonyl or sulphonyl group substituted by a C_{1-8}-alkyl group or by a C_{3-7}-cycloalkyl, phenylC_{1-3}-alkyl or phenyl group, wherein each phenyl moiety in R_5 is optionally mono- or disubstituted by fluorine, chlorine or bromine atoms, by trifluoromethyl groups, or by C_{1-3}-alkyl, C_{1-3}-alkoxy, C_{1-3}-alkylsulphenyl, C_{1-3}-alkylsulphinyl or C_{1-3}-alkylsulphonyl groups and the substituents may be identical or different;

wherein

(i) if the A-B- moiety denotes a phenyl group substituted in the 4-position by an R_b-NH-CH_2- group wherein R_b is a benzyloxycarbonyl group, then R_aOOC-E-D-C- does not denote a 3-carboxy-phenylaminocarbonyl group,

(ii) if the A-B- moiety denotes a phenyl group substituted in the 4-position by an R_b-NH-CH_2- group wherein R_b denotes a hydrogen atom or an acetyl group, then R_aOOC-E-D-C- does not represent a phenylcarbonyl group substituted in the 4-position by a carboxymethyl, methoxycarbonylmethyl, 2-carboxy-ethyl, 2-

methoxycarbonyl-ethyl or 2-ethoxycarbonylethyl group,

(iii) if the A-B- moiety denotes a phenyl group substituted in the 4-position by an $NH_2-CH_2-CH_2-$ group, then $R_aOOC-E-D-C-$ does not denote a 4-ethoxycarbonyl-phenylcarbonyl group,

(iv) if the A-B- moiety denotes a 4-aminomethyl-phenyl-, 3-aminomethyl-phenyl-, 4-aminomethyl-3-methoxy-phenyl- or 3-aminomethyl-4-methoxyphenyl group, then $R_aOOC-E-D-C-$ does not denote a 4-ethoxycarbonylmethoxy-2,3-dichlorophenylcarbonyl group,

(v) if the A-B- moiety denotes a phenyl group substituted in the 4-position by an NH_2-CH_2- or $(CH_3)_3CO-CO-NH-CH_2-$ group, then $R_aOOC-E-D-C-$ does not denote a 4-carboxyphenylmethoxy group,

(vi) if the A-B- moiety denotes a phenyl group substituted in the 4-position by an NH_2-CH_2- group, then $R_aOOC-E-D-C-$ does not denote a 4-carboxy-phenylaminosulphonyl group,

(vii) if the A-B- moiety denotes a 4-(2-pyridyl)-phenyl- or 4-(3-pyridyl)-phenyl group, then $R_aOOC-E-D-C-$ does not denote a 4-carboxy-phenylcarbonylamino, 4-benzyloxycarbonyl-phenylcarbonylamino- or 2-(4-carboxy-phenyl)-ethyl group, and

(viii) if the A-B- moiety denotes a 3-(4-pyridyl)-phenyl group, then $R_aOOC-E-D-C-$ does not denote a 2-(carboxymethyl)-phenylcarbonylamino group)

and the isomers and salts thereof.

2. Compounds of formula I according to claim 1, wherein

R_a denotes a hydrogen atom or a C_{1-5}-alkyl, phenyl(C_{1-3}-alkyl) or C_{5-7}-cycloalkyl group;

A denotes a C_{2-5}-aminoalkyl group linked to group B via a carbon atom of A, or a piperidinyl group linked to group B via a carbon atom of the piperidinyl group, or A denotes a quinuclidinyl or pyridyl group, wherein the nitrogen of the above-mentioned aminoalkyl or piperidinyl groups is optionally substituted by a group R_b, wherein the carbon atoms of the piperidinyl group are optionally substituted by methyl, cyano, carboxy, methoxycarbonyl or aminocarbonyl groups,

and wherein in a piperidinyl A group a >CH- unit in the 4-position may be replaced by a nitrogen atom or a $-CH_2-CH<$ unit may be replaced by a -CH=C< unit;

R_b denotes a C_{1-3}-alkyl, benzyl, (C_{1-5}-alkoxy)carbonyl, benzyloxycarbonyl or $CH_3-CO-O-(CH_2)-O-CO-$ group;

B denotes a phenylene group optionally substituted by a fluorine, chlorine or bromine atom or by a C_{1-2}-alkyl, C_{1-2}-alkoxy, C_{1-2}-alkylsulphenyl, C_{1-2}-alkylsulphinyl or C_{1-2}-alkylsulphonyl group, or B denotes a pyridinylene or piperidinylene group;

C denotes a $-CO-$, $-CH_2CH_2-$, $-CH=CH-$, $-CH_2-$, $-CH_2O-$, $-OCH_2-$, $-CONR_4-$, $-NR_4CO-$, $-NR_4CO-NR_4-$, $-CH_2NR_4-$, $-NR_4CH_2-$, $-SO_2NR_4-$ or $-NR_4SO_2-$ group;

R_4 denotes a hydrogen atom or a C_{1-2}-alkyl or phenyl(C_{1-2}-alkyl) group or, if C denotes a $-CONR_4$ group bound to group B via the carbonyl group, R_4 may also denote a methylene or 1,2-ethylene group bound to the carbon atom of group B in the ortho- position relative to the point of linkage of the $-CONR_4$ group;

D denotes a phenylene group optionally substituted by a chlorine or bromine atom, or by a C_{1-2}-alkyl or C_{1-2}-alkoxy group, or D denotes a cyclohexylene group in which one or two >CH- units may be replaced by N-atoms, and additionally, in a piperidinylene or piperazinylene D group a ring carbon adjacent to a ring nitrogen is optionally oxo-substituted;

E denotes a bond, a methyleneoxy group bound to group D through the oxygen atom, a 1,2-ethenylene group or a straight-chain C_{1-5}-alkylene group which may be substituted by a C_{1-7}-alkyl group or by an R_5NH- group; and

R_5 denotes a hydrogen atom or a C_{1-7}-alkylcarbonyl, benzylcarbonyl, C_{1-5}-alkylsulphonyl or benzylsulphonyl group;

wherein

(iii) if the A-B- moiety denotes a phenyl group substituted in the 4-position by an $NH_2-CH_2-CH_2$- group, then R_aOOC-E-D-C does not denote a 4-ethoxycarbonyl-phenylcarbonyl group, and

(vii) if the A-B- moiety denotes a 4-(2-pyridyl)-phenyl- or 4-(3-pyridyl)-phenyl group, then R_aOOC-E-D-C- does not denote a 4-carboxy-phenylcarbonylamino, 4-benzyloxycarbonyl-phenylcarbonylamino- or 2-(4-carboxy-phenyl)-ethyl group, and

(viii) if the A-B- moiety represents a 3-(4-pyridyl)-phenyl group, then R_aOOC-E-D-C- does not denote a 2-(carboxymethyl)-phenylcarbonylamino group;

and the tautomers, stereoisomers and salts thereof.

3. Compounds of formula I according to claim 1, wherein

R_a denotes a hydrogen atom or a C_{1-4}-alkyl, 2-phenylethyl or cyclohexyl group;

A denotes a C_{3-5}-aminoalkyl group linked to group B via a carbon atom of A, or a piperidinyl group linked to group B via a carbon atom of the piperidinyl group or A denotes a quinuclidinyl or 4-pyridyl group, wherein the nitrogen atom in the above-mentioned piperidinyl group is optionally substituted by a group R_b, wherein the carbon atoms of the piperidinyl group are optionally substituted by methyl, cyano, carboxy, methoxycarbonyl or aminocarbonyl groups,

and wherein in a piperidinyl A group a >CH- unit in the 4-position may be replaced by a nitrogen atom or a $-CH_2-CH<$ unit may be replaced by a -CH=C< unit;

R_b denotes a C_{1-3}-alkyl, benzyl, (C_{1-4}-alkoxy)carbonyl or $CH_3-CO-O-(CH_2)-O-CO-$ group;

B denotes an optionally methyl- or methoxy- substituted phenylene group or a 2,5-pyridinylene or 1,4-piperidinylene group;

C denotes a $-CO-$, $-CH_2CH_2-$, $-CH=CH-$, $-CH_2-$, $-CH_2O-$, $-OCH_2-$, $-CONR_4-$, $-NR_4CO-$, $-NR_4CO-NR_4-$ or $-CH_2NR_4-$ group or an $-SO_2NR_4-$ group wherein the SO_2 moiety is linked to group B;

R_4 denotes a hydrogen atom or a methyl or 2-phenylethyl group or, if C denotes a $-CONR_4-$ group bound to group B via the carbonyl group, R_4 may also denote a methylene or 1,2-ethylene group bound to the carbon atom of group B in the ortho-position relative to the linkage point of

the $-CONR_4-$ group;

D denotes a phenylene group or a cyclohexylene group in which one or two >CH- units may be replaced by N- atoms;

E denotes a bond, a methyleneoxy group bound to group D through the oxygen atom, or a straight-chain C_{1-5}-alkylene group which may be substituted by an R_5NH- group;

R_5 denotes a hydrogen atom or a (C_{1-5}-alkyl)carbonyl, C_{1-4}alkyl-sulphonyl, or benzylsulphonyl group;

and the tautomers, stereoisomers and salts thereof.

4. Compounds of formula I according to claim 1, wherein

R_a denotes a hydrogen atom or a C_{1-4}-alkyl or cyclohexyl group;

A denotes a piperidinyl or 3,4-dehydro-piperidinyl group linked to group B via the 4-position, wherein the nitrogen atom is optionally substituted by a group R_b or A denotes a 4-piperazinyl group optionally substituted by a group R_b in the 1-position, or A denotes a quinuclidinyl group;

R_b denotes a (C_{1-4}-alkoxy)carbonyl group;

B denotes a phenylene group;

C denotes a $-CONR_4$ group;

R_4 denotes a hydrogen atom or a methyl group or, if C denotes a $-CONR_4$ group bound to group B via the carbonyl group, R_4 may also represent a methylene or 1,2-ethylene

group bound to the carbon atom of group B in the ortho-position relative to the point of linkage of the $-CONR_4$ group;

D denotes a 1,4-phenylene or 1,4-cyclohexylene group;

E denotes a bond or a 1,2-ethylene group optionally substituted by an R_5NH- group; and

R_5 denotes a (C_{1-5}-alkyl)carbonyl or a C_{1-4}-alkylsulphonyl group;

and the tautomers, stereoisomers and salts thereof.

5. Compounds of formula I according to claim 1 being

4-[4-[[trans-4-[2-(methoxycarbonyl)-ethyl]-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine,

4-[4-[[4-[2-(n-butanesulphonylamino)-2-(methoxycarbonyl)-ethyl]-phenyl]-aminocarbonyl]-phenyl]-piperidine,

4-[4-[[trans-4-(2-carboxyethyl)-cyclohexyl]-aminocarbonyl]-phenyl]-piperidine,

4-[4-[[4-[2-(n-butanesulphonylamino)-2-carboxyethyl]-phenyl]-aminocarbonyl]-phenyl]-piperidine,

4-[3-[[4-[2-(n-butanesulphonylamino)-2-carboxyethyl]-phenyl]-aminocarbonyl]-phenyl]-piperidine and

4-[3-[[4-[2-(n-butanesulphonylamino)-2-(methoxycarbonyl)-ethyl]-phenyl]-aminocarbonyl]-phenyl]-piperidine,

and the tautomers, stereoisomers and salts thereof.

6. A compound as claimed in any one of claims 1 to 5 in the form of a physiologically acceptable addition salt with an inorganic or organic acid or base.

7. A pharmaceutical composition comprising a compound of formula I as claimed in any one of claims 1 to 5 or a physiologically acceptable addition salt thereof together with at least one physiologically acceptable carrier or excipient.

8. A process for preparing a compound as claimed in any one of claims 1 to 5, said process comprising at least one of the following steps:

a) (to prepare compounds of formula I wherein R_a denotes a hydrogen atom) hydrolysing, pyrrolysing or hydrogenolysing a compound of formula II

$$A - B - C - D - E - COOR_a' \qquad (II)$$

(wherein
A, B, C, D and E are defined as in any one of claims 1 to 5 and
R_a' has the meanings given for R_a in any one of claims 1 to 5, with the exception of the hydrogen atom);

b) (to prepare compounds of formula I wherein A is substituted by a group R_b) reacting a compound of formula III

$$A_1 - B - C - D - E - COOR_a \qquad (III)$$

(wherein
B, C, D, E and R_a are as defined in any one of claims 1 to 5 and
A_1 denotes a C_{1-5}-aminoalkyl group linked to group B via a carbon atom or a 5-, 6- or 7-membered azacycloalkyl

group linked to group B via a carbon atom, wherein the carbon atoms of the azacycloalkyl group may be substituted by one, two, or three C_{1-3}-alkyl groups, or by an aminocarbonyl, cyano, R_3O- or R_3O-CO- group (wherein R_3 is defined as in any one of claims 1 to 5)) with a compound of formula IV

$$R_b - Z_1 \qquad (IV)$$

(wherein
R_b is defined as in any one of claims 1 to 5 and
Z_1 denotes a nucleophilic leaving group
or, if Z_1 is bound to a carbonyl group, it may also denote a hydroxy, alkanoyloxy or alkoxycarbonyloxy group,
or in the presence of a reducing agent when Z_1 together with an adjacent hydrogen atom of the group R_b denotes an oxygen atom);

c) (to prepare compounds of formula I wherein R_a is defined as in any one of claims 1 to 5 with the exception of the hydrogen atom) reacting a compound of formula V

$$A - B - C - D - E - COOH \qquad (V)$$

(wherein
A, B, C, D and E are defined as in any one of claims 1 to 5) with a compound of formula VI

$$Z_2 - R_a' \qquad (VI)$$

(wherein
R_a' has the meanings given for R_a in any one of claims 1 to 5, with the exception of the hydrogen atom, and
Z_2 denotes a nucleophilic leaving group);

d) (to prepare compounds of formula I wherein C denotes a $-CH_2-NH-$ group) reducing a compound of formula VII

$$A - B - CH=N - D - E - COOR_a \qquad (VII)$$

(wherein
A, B, D, E and R_a are defined as in any one of claims 1 to 5);

e) (to prepare compounds of formula I wherein C denotes a $-CO-NR_4-$ group) reacting a compound of formula VIII

$$A_2 - B - COOH \qquad (VIII)$$

(wherein
B is defined as in any one of claims 1 to 5 and
A_2 denotes a group A substituted at the nitrogen atom by an alkyl, aralkyl, alkanoyl, trifluoroacetyl or alkoxycarbonyl group) with an amine of formula IX

$$R_4 - NH - D - E - COOR_a' \qquad (IX)$$

(wherein
D, E and R_4 are defined as in any one of claims 1 to 5 and
R_a' has the meanings given for R_a in any one of claims 1 to 5, with the exception of the hydrogen atom);

f) (to prepare compounds of formula I wherein C denotes an $-NR_4-CO-$ group) reacting a compound of formula X

$$A_2 - B - NH-R_4 \qquad (X)$$

(wherein
R_4 and B are defined as in any one of claims 1 to 5 and
A_2 denotes a group A substituted at the nitrogen atom by an alkyl, aralkyl, alkanoyl, trifluoroacetyl or alkoxycarbonyl group) with a carboxylic acid of formula XI

$$HOOC - D - E - COOR_a' \qquad (XI)$$

(wherein
D and E are defined as in any one of claims 1 to 5 and R_a' has the meanings given for R_a in any one of claims 1 to 5 with the exception of the hydrogen atom);

g) (to prepare compounds of formula I wherein A denotes a C_{1-5}-aminoalkyl group linked to group B via a carbon atom) reducing a compound of formula XII

$$A_3 - B - C - D - E - COOR_a \qquad (XII)$$

(wherein
B, C, D, E and R_a are defined as in any one of claims 1 to 5 and A_3 denotes a cyano or cyanoC_{1-4}alkyl group);

h) (to prepare a compound of formula I wherein R_4 denotes a C_{1-2}-alkyl group optionally substituted by a phenyl group) alkylating a compound of formula I wherein R_4 denotes a hydrogen atom;

i) performing the process of any one of steps (a) to (h) above on a reagent having a protecting group and subsequently removing the protecting group used;

j) converting a compound of formula I into a salt thereof; and

k) resolving a compound of formula I into its isomers.

9. The use of a compound of formula I as claimed in any one of claims 1 to 5 or a physiologically acceptable salt thereof for the manufacture of a medicament for use in combating inflammation, bone degradation, tumours, metastases, thrombosis and aggregation-related conditions.

10. A method of treatment of the human or non-human animal body to combat inflammation, bone degradation, tumours, metastases, thrombosis and aggregation-related conditions, said method comprising administering to said body a commpound of formula I as defined in any one of claims 1 to 5 or a physiologically acceptable salt thereof.

11. Each and every novel compound, composition, process, method and use herein disclosed.

D A T E D this 8th day of December, 1993.

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Abstract

Carboxylic acid derivatives

The invention relates to carboxylic acid derivatives of formula I

$$A - B - C - D - E - COOR_a \qquad (I)$$

wherein
A to E and R_a are defined as in claim 1, the tautomers thereof, the stereoisomers thereof including the mixtures thereof and the salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases, which have valuable pharmacological properties, particularly inhibitory effects on aggregation.